**KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI**
**COLLEGE OF SCIENCE**

**FACULTY OF PHYSICAL SCIENCE**

**DEPARTMENT OF MATHEMATICS**

# MODELING KINETICS OF LEAD IN THE HUMAN BODY USING FIRST ORDER ORDINARY DIFFERENTIAL EQUATIONS

**BY**

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**MAY ,2014**

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A thesis Submitted to the Department of Mathematics, Kwame Nkrumah University of Science and Technology, Kumasi, in Partial Fulfillment of the requirements for the Degree of Bachelor of Science in Mathematics

**MAY ,2014**

# DECLARATION

We hereby declare that this submission is our own work towards the award of a degree in BSc Mathematics and that, to the best of our knowledge, it contains no material(s) previously published by another person(s) nor material(s), which have been accepted for the award of any other degree of the University except where the acknowledgement has been made in the text.

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# DEDICATION

To our family and friends

# ABSTRACT

A mathematical model is a description of a system using mathematical concepts and language. The process of developing a mathematical model is termed mathematical modeling. Mathematical models are used not only in engineering disciplines (e.g. computer science, artificial intelligence) and in the social sciences (such as economics, psychology, sociology and political science), but also the natural sciences(such as physics, biology, earth science, meteorology). Physicists, engineers, statisticians, operations research analysts and economists use mathematical models most extensively. A model may help to explain a system and to study the effects of different components, and to make predictions about behavior. This study aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools. It has both theoretical and practical applications in biological, biomedical and biotechnology research.

Lead is an important metal as far as modernization and industrialization is concern. Despite its relevance, it is a very strong poison. When a person swallows a lead object or breathes in lead dust, some of the poison can stay in the body and cause serious health problems. Here the body is divided into three compartments; the blood stream, the tissue and the bone. The model focuses on the rate of exchange of lead in the three compartments. We then determine the steady state solution, stability analyses and how the various compartments react to reasonable medical assumptions with graphical output from Mat lab.

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## ACRONYMS

μg/dL……. …….Micrograms per deciliter

WHO……World Health Organisation

BLL…….Blood Lead Level

NTP…….National Toxicity Program

EPA…… Environmental Protection Agency

ALAD……..Aminolevulinate Dehydrature

AAP……Association of American Publisher's

IARC…….....International Agency for Research on Cancer

ATSDR…….Agency for Toxic Substances and Disease registry

# CHAPTER ONE

## Background of the Study

The study of differential equations has attracted the attention of many of the world's greatest mathematicians for the past three centuries. Nevertheless, it remains a dynamic field of inquiry today with many interesting open questions. Differential equation has become very useful tool in mathematics today and it plays an important role in modeling physical processes, from celestial motion, bridge design to interaction between systems. Its principles are applied not only in natural sciences (Physics, Chemistry, Biology etc.) and Engineering disciplines, but also in Social sciences (Sociology, Economics, Administration, etc.) to solve many of the world's problems.

The subject of differential equations is solving problems and making predictions. In this material, we will exhibit some of these examples which are applied in physics, chemistry, and biology, and also in such areas as personal finance and forensics. This is the process of mathematical modeling. If it were not true that differential equations were so useful, we would not be studying them, so this is the reason why we selected a project under this course in order to expose some of its application to the one reading this material especially on the modeling process and with specific models. It must be observed that, the study of differential equations, and their application, uses the derivative and the integral, the concepts that make up the calculus.

## 1.1 Lead

The industrial and urbanization is gaining momentum at a cost of incurring environmental degradation, lead is a naturally occurring element found in the earth crust, its soft, blue-grey metallic element, its atomic number is 82 and atomic mass of 207.19. It is very soft, highly malleable, ductile, and a relatively poor conductor of electricity, it is very resistant to corrosion

but tarnishes upon exposure to air. Lead pipes bearing the insignia of Roman emperors, used as drains from baths, are still in service. We have the inorganic lead compounds and the organic lead compounds. Organic lead refers to lead compounds which contain carbon while inorganic lead refers to lead compounds including elemental lead, which do not contain carbon.

In fact it's the heaviest stable metal known. In its metallic form, lead is used as a protective shielding against x-rays and it still used in bullets because it is dense and heavy enough to reach the necessary trajectory speed without having to make cumbersomely large. Lead is poisonous, a characteristics that has led to a reduction in the use of lead compounds as pigment for plants and inks. Normal concentration in the whole blood is 0 and 5µg/dL. The normal amount in the urine after 24 hours collection is less than 100 µg. Whiles it has its advantages; when exposed to lead accidentally or intentionally can be detrimental to human health.

**1.2 Exposure of Lead**

Today almost everyone is exposed to environmental lead; it is found in most part of our environment; in the air, soil, water. Lead mining and lead smelting are common in many countries, where children and adults can receive substantial lead exposure from sources uncommonly in the world. Activities of human such as the use of fossil fuels, it's also found in and around our homes including paint, ceramics, pipes, plumbing materials, solders, gasoline, batteries, ammunitions, handmade pottery, traditional medicine and cosmetics. Lead absorb by children is higher than in adult, and lead also enter the environment through activities such as mining. For most people who are not exposed continuously by inhalation is minimal with ingestion of food containing traces of lead being the maximum source of lead for adult population. Lead can also be emitted into the environment from industrial sources and contaminated sites, such as former lead smelters.

When lead is released to the air from industrial sources or vehicles, it may travel long distances before settling to the ground, where it usually sticks to soil particles. Lead may move from soil into ground water depending on the type of lead compound and the characteristics of the soil.

### 1.2.1 Inhalation Exposure

The uptake of lead can occur through inhalation. For most people who are not exposed occupationally exposure by inhalation route will be minimal. Inhaling lead dust from the air is a common way lead gets into the body. Airborne lead however, represents an important source of lead exposure in children when deposited in dust and dirt. However, different studies reach different assessments of contribution of air lead to food lead and hence body burden (Royal Commission on Environmental Pollution, 1983). Also, dust contributes to a greater proportion of lead to the background body burden of young children than to adults and older children. It has been calculated that, dust contributes only 7 to 11% of the baseline lead in adults, but 44% in 2-years old children (Elias 1985).Smaller particles can reach deeper in the lungs and from there be absorbed into the blood stream, and then the person's blood lead levels will begin to rise.

### 1.2.2 Ingestion Exposure

Apart from inhalation, lead can also be ingested through the food we eat and hand to mouth activity from lead in dust and soil. Drinking water may contain lead if it flows through lead pipes or fittings. Research has shown that among the higher food intake relative to size and the higher metabolic level and greater motor activity compared to higher dietary lead consumption (Mahaffey 1985). Reported intake of lead from food are quite variable (WHO,1977). Among inhalation and dermal exposure, ingested food containing traces of lead is the main source of lead exposure for the general adult's population (Thornton et al. 2001). Lead paint is the major source of lead exposure for children. (AAP 1993; ATSDR 2005) As lead paint deteriorates,

peels, chips, or is removed (e.g. by renovation), or pulverizes due to friction (e.g., in windowsills, steps and doors), house dust and surrounding soil may become contaminated. Lead then enters the body through the normal hand-to-mouth activity (Sayre et al. 1974 as cited in AAP 1993). It commonly done by children who picks things from the ground and put into their mouth, some also play with toys with lead paints. Also pregnant women sometimes crave for things that may contain lead in them such as clay, chalk etc. it might also get in the system by taking food in home-made pottery, or using utensils that rust. Most cosmetics used by ladies also contain lead and they may get into the system accidentally.

### 1.2.3 Dermal Exposure

Apart from inhalation and ingestion, dermal exposure is also a source of lead uptake into the body .Dermal uptake of lead is thought to be of minimal importance, however, dermal is still important as it can contribute to ingestion exposure due to transfer from the skin to the mouth via the fingers. The rate of permeation of lead through the skin will be minimal and depends on the form of lead, with higher rate likely for more than soluble forms of inorganic lead (Stauber et al. 1994). It plays a role for exposure to organic lead among workers but not considered significant pathway for the general population. It is when lead sheet materials get direct contact with the skin; organic lead is more likely to be absorbed through the skin than inorganic lead. Also a number of publications have shown a significant positive association between dermal lead exposure and blood lead level (Askin and Volkmann 1997; Sun et al. 2002). The total amount of lead stored in the body is referred to as “body burden”. In adults, bones and teeth contain 95% of the body burden. When lead is removed from medical treatment it’s called chelation.

### 1.3 Health Implication of Lead

Lead poisoning was first known to the Roman's, but they didn't take it serious. They even used to mix powdered lead with wine to make it thick, heavy and sweet. Lead poisoning occurs when lead builds up in the body, often over a period of months or years. Even small amounts of lead can cause serious health problems. Children under the age of 6 are especially vulnerable to lead poisoning, which can severely affect mental and physical development. At very high levels, lead poisoning can be fatal. Lead when in large quantities can be very dangerous to human health; it can affect almost every organ and system in the body. Lead poisoning causes systematic effect like renal effects, neurological effects, reproduction effect, and cardiovascular (hypertension) effects and can lead to cancer and death.

### 1.4 Systematic Effects

Systematic effects include kidney damage, which can lead to high blood pressure and bone marrow damage, which can cause anaemia (low red blood cell count)

#### 1.4.1 Renal Effects

Many studies show a strong association between lead exposure and renal effects (ATSDR 1999). Acute high dose lead-induced impairment of proximal tubular function manifests in aminoaciduria, glycosuria, and hyperphosphaturia. These effects appear to be reversible (ATSDR 1999). However, continued or repetitive exposures can cause a toxic stress on the kidney, if unrelieved, may develop into chronic and often irreversible lead nephropathy (*i.e.*, chronic interstitial nephritis). Latent effects of lead exposure that occurred years earlier in childhood may cause some chronic advanced renal disease or decrement in renal function. Lead exposure is also believed to contribute to "saturnine gout," which may develop because of lead-induced hyperuricemia due to decreased renal excretion of uric acid. In one study, more than

50% of patients suffering from lead nephropathy also suffered from gout (Bennett 1985 as cited in ATSDR 2000). Saturnine gout is characterized by less frequent attacks than primary gout. Lead-associated gout may occur in pre-menopausal women, an uncommon occurrence in non-lead associated gout (Goyer 1985, as cited in ATSDR 2000).

### 1.4.2 Neurological Effects

Once lead enters into the body, it interferes with normal cell function and physiological effects of lead include harm done to the peripheral and central nervous system (PNS, CNS), the nervous system seems to be the most sensitive to lead poisoning. Lead can block the release of neurotransmitters when the action potential is taking place. The effect of lead can have serious consequences on a developing nervous system, the development process can be inhibited and have permanent effects on synaptic anatomy and function of the brain. It is believed that this is one of the causes of learning and behavioural problems that occur in children. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Kumar et al. 1987).

### 1.4.3 Reproduction Effect

Reproductive effects examined in the literature include sperm count, fertility, and pregnancy outcomes. While several studies have implicated lead as contributing to reproductive and developmental effects, these effects have not been well-established at low exposure level. Recent reproductive function studies in humans suggest that current occupational exposures decrease sperm count totals and increase abnormal sperm frequencies (Alexander *et al.* 1996; Telisman *et*

*al.* 2000). Epidemiological studies have shown that exposure of pregnant women to lead increases the risk of preterm delivery (WHO 2011). In a study of 774 pregnant women in Port Pirie who were followed to the completion of their pregnancy, the relative risk of preterm delivery was more than 4 times higher among women with blood lead levels above 14 µg/dl than in those with 8 µg or less per deciliter (WHO 2011).Long-term lead exposure (independent of current lead exposure levels) also may diminish sperm concentrations, total sperm counts, and total sperm motility (Alexander et al. 1996 as cited in ATSDR 2000).

### 1.4.4 Cardiovascular (Hypertension) Effects

Hypertension is a complex condition with many different causes and risk factors, including age, weight, diet, and exercise habits. Lead exposure is one factor of many that may contribute to the onset and development of hypertension. Although low to moderate lead level exposures (BLL<30 µg/dL) show only a low degree of association with hypertension, higher exposures (primarily occupational) increase the risk for hypertensive heart disease and cerebrovascular disease as latent effects. One study found that adults who experienced lead poisoning as children had a significantly higher risk of hypertension 50 years later (relative to control adults without childhood lead exposure). (Hu, 1991, as cited in ATSDR 2000) The association has been shown in population-based studies with BLLs below 10 µg/dL. Data supports an association between lead exposure and elevations in blood pressure. (Victery et al. 1988; Schwartz 1995 as cited in ATSDR 2000; Korrick et al. 1999).It is estimated that, on a population basis, blood lead can account for a 1% to 2% variance in blood pressure (ATSDR 2000). This could increase the incidence of hypertension a substantial amount, due to the high prevalence of hypertension of all causes in general populations.

### 1.4.5 Cancer

Several agencies study different substances in the environment to determine if they can cause cancer. The American Cancer Society looks to these organizations to evaluate the risks based on evidence from laboratory, animal, and human research studies.

Based on the available evidence, some of these expert agencies have evaluated the cancer-causing potential of lead and lead compounds. Exposures that are thought to be carcinogenic are included in the Report on Carcinogens, published every few years (NTP). The NTP classifies lead and lead compounds as "reasonably anticipated to be human carcinogens. The IARC is part of the World Health Organization (WHO). Its major goal is to identify causes of cancer. The IARC has classified inorganic lead compounds as "probably carcinogenic to humans," based on limited evidence in humans and sufficient evidence in lab animals. Organic lead compounds are listed as "not classifiable as to their carcinogenicity in humans," based on inadequate evidence. Also the EPA maintains the Integrated Risk Information System (IRIS), an electronic database that contains information on human health effects from exposure to various substances in the environment. The EPA has classified lead and inorganic lead compounds as "probable human carcinogens." Most of the studies found an increased risk of stomach cancer with higher lead exposure. Several studies have also looked for a link between exposure to lead in the workplace (mainly among battery workers and smelter workers) and lung cancer. Some of these studies have found a small increase in lung cancer risk. Some studies looking at blood lead levels in the general population have also found a small increased risk of lung cancer.

### 1.4.6 Death

At very high levels, lead poisoning can cause seizures, coma and even death. At extreme levels of exposure, lead can severely damage the brain and kidneys in adults or children and ultimately causes death. Three additional studies provided suggestive evidence of increased mortality due to cerebrovascular disease in lead workers ( Malcolm and Barnett 1982)

## 1.5 Distribution of lead in the body

Lead appears to be distributed essentially the same manner, regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987). The expression, body burden is used here to refer to the total amount of lead in the body. Most of the available information about the distribution of lead to major organ systems (e.g., bone, soft tissues) is derived from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when exposure levels were much higher than current levels. (Barry 1975). In general, these studies indicate that the distribution of lead appears to be similar in children and adults, although a larger fraction of the lead body burden of adults resides in the bone. Here we shall discussed the distribution of lead in the Blood, Tissue and Bone.

### 1.5.1 Blood

Distribution of lead in blood vary considerably with age, physiological state (e.g., pregnancy, lactation, and menopause) and numerous factors. Although the blood generally carries only a small fraction of total lead body burden, it does serve as the initial receptacle of absorbed lead and distributes lead throughout the body, making it available to other tissues. The excretory half-life of lead in the blood, in adult humans, is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976). Approximately 99% of the lead in blood is associated with red blood cells; the remaining 1% resides in blood plasma. (DeSilva 1981; EPA,

1986a; Everson and Patterson, 1980, as cited in ATSDR, 1999). Most of the lead found in red blood cells is bound to proteins within the cell rather than the erythrocyte membrane.

### 1.5.2 Tissue

Several studies have compared concentrations of lead in autopsy samples of soft tissues. (Barry 1975)reported that average PbBs in the adult subjects were approximately 20 μg/dL. Levels in other soft tissues also appear to have decreased substantially since these studies were reported. For example, average lead concentrations in kidney cortex of male adults were 0.78 μg/g wet tissue as reported by Barry (1975). (samples in the Barry study were from subjects who had no known occupational exposures). In spite of the downward trends in soft tissue lead levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of lead in adults and children. Most of the lead in soft tissue is in the liver. Relative amounts of lead in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue lead, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975)

### 1.5.3 Bone

In adults, approximately 94% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975). Lead concentrations in bone increase with age throughout the lifetime, indicative of a relatively slow turnover of lead in adult bone (Barry 1975, Schroeder and Tipton 1968). This large pool of lead in adult bone can serve to maintain blood lead levels long after exposure has ended ( Kehoe 1987; O'Flaherty et al. 1982). It can also serve as a source of lead transfer to the fetus when maternal bone is reabsorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Although a high bone formation rate in early childhood results in the rapid uptake of circulating lead into mineralizing bone, bone lead is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the lead acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone lead levels among adults (Barry 1975; Schroeder and Tipton 1968).

During pregnancy, the mobilization of bone lead increases, apparently as the bone is catabolized to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood lead in pregnant women as they came into equilibrium with a novel environmental lead isotope signature indicated that 10–88% of the lead in blood may derive from the mobilization of bone lead stores and approximately 80% of cord blood may be contributed from maternal bone lead ( Gulson et al. 1997b,).

**1.6 Excretion of lead from the human body**

Independent of the route of exposure, absorbed lead is excreted primarily in urine and feces; sweat, saliva, hair and nails, and breast milk are minor routes of excretion (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed lead (fecal/urinary

excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of lead particles (Chamberlain et al. 1978; Hursh et al. 1969).

### 1.7 Metabolism of lead in the body

Metabolism of lead consists of formation of complexes with a variety of protein and nonprotein ligands. Major extracellular ligands include albumen and nonprotein sulfhydryls. The major intracellular ligand in red blood cells is ALAD. Lead also forms complexes with proteins in the cell nucleus and cytosol.

Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead (Zhang et al. 1994).

### 1.8 Problem Statements

Lead is an important metal as far as modernization and industrialization is concern. Despite its relevance it is a cumulative toxicant that affects multiple body systems and harmful to humans especially children and hence the need to study the behaviour and the concentration at the steady state to help reduce the lead content in human body through medical delivery.

### 1.9 Objectives

The main aim of the study is to determine the amount of lead in the body in the steady state and the sensitivity analysis of lead in the three compartments.

### 1.10 Limitations

To get data for this study, we needed to study a subject for some time. Due to time and financial constraints to study a subject in Ghana the data was obtained from Southern California through the internet.

### 1.11 Organization

This study is divided into five chapters, chapter one comprises of the background study of lead. Chapter two entails the literature review and short study of differential equations. Chapter three comprises the schema and modeling of the system. The solution and analysis of the model is done in chapter four. Lastly the conclusion and recommendation is also done in chapter five.

# CHAPTER TWO

## Literature review

There have been numerous lead biokinetic models to assess the relationship between environmental lead exposures and blood lead (PbB) concentration in humans. Despite the good work by various authors they have distinct weaknesses. Most of these models are multi-compartment models which simulate lead biokinetic as one or several interconnected tissue compartments that exchange lead through central blood or plasma compartment. The exchanges in both models are modeled by first order differential equations.

The O'Flaherty model is an extension and modification of an earlier model of lead biokinetics in the rat (O'Flaherty, 1991a,b). The only difference is that it simulates the delivery of lead to tissues as a function of blood flow to the tissues. The central plasma compartment has dimensions of volume and flow, and transfers of lead from the central plasma compartment are simulated as entirely, or partially, perfusion-limited processes.

O'Flaherty (1993) modeled the kinetics of exchange of lead between plasma and bone as three interdependent processes that occur in series: flow-limited exchange with surface bone, exchange between plasma leaving the bone surface and the metabolically active region of bone, limited by age-dependent rates of bone formation reabsorption and exchange between plasma leaving the metabolically active region of bone and mature bone (where rates of bone formation and reabsorption are low), limited by diffusion (representing ionic exchange of lead and calcium).

The 1993 version of the model was subsequently modified (O'Flaherty, 1995, 1997) as follows to include separate compartments for cortical and trabecular bone, based on results of

pharmacokinetic studies conducted in non-human primates: the separate module representing exchange with surface bone was eliminated, exchanges between plasma and metabolically active trabecular and cortical bone were modeled as separate parallel processes and cortical bone was represented as containing both metabolically active regions of bone formation and reabsorption as well as a region of lead-calcium exchange, which receives blood leaving the metabolically active region of cortical bone. Exchanges between plasma and bone are represented as age-dependent processes by their linkage to variables that represent age-dependent rates of bone formation and reabsorption.

The model simulates PbB concentrations for ages from birth through adulthood, the model simulates both short-term and long-term exposures, the model can also simulate biokinetics of females or males, the model calculates tissue lead accumulation in any compartment for any age range, the model simulates nonlinear kinetics of lead in blood and can be calibrated to achieve a reasonable fit to epidemiologic and experimental data.

The major limitations of the model include relatively weak empirical support for some of the model components; the model is not designed to simulate maternal biokinetics during pregnancy; the exposure module for adults is limited to age-specific intakes; and a variety of limitations in the C++ code, including limited graphics capability, cumbersome user interface, and limited access to certain variables and constants. Moreover, the program crashes when certain combinations of simulation durations and communication intervals are selected.

Rabinowitz et al. (1976) model simulate changes in blood lead concentrations in adult males in response to lead uptakes. Their data was collected from five healthy subjects who received oral doses of stable lead isotopes for various period of time. This was divided into three compartments: the tissue compartment, the blood or plasma compartment and the bone

compartment representing kinetically different lead pools in the body. The model was designed and calibrated to predict quasi-steady state blood lead concentrations.

The model was designed and calibrated to predict quasi-steady state blood lead concentrations corresponding to long-term exposure. PbB concentrations corresponding to intermittent exposures can be calculated easily with the model. Rabinowitz model parameter values are for adult males and not age-specific.

Therefore, exposure to lead during infancy, childhood or adolescence cannot be simulated.

Also, changes in lead biokinetics that may occur during pregnancy are not simulated. Exposure and uptake are modelled; hence external model could be linked to the biokinetic model. Also, variability is not modelled; however, any external model for variability could be linked to the biokinetic model.

Rabinowitz et al.1976 work was extended by Batschelet et al.1979.The data from this study were used to estimate the rate constants for the compartment model.

In addition, Bert et al. (1989) model estimates the lead body burden associated with intakes of lead to the gastrointestinal and respiratory tracts for a typical adult male. The central compartment represents whole blood and other spaces that rapidly equilibrate with lead in whole blood. The model is designed to predict lead in major body compartments. It predicts the mass of lead in blood, cortical bone, trabecular bone, and other tissues combined. The model also predicts the amount of lead excreted through the urine.

Stern also developed two models to assess risks from exposures to lead in soil using different scenarios, receptors, and toxicological endpoints. The Stern (1994) model was developed for

residential land use scenarios; the exposed population of concern is children ages 1–7 years; and the measured endpoint is the incremental increase in blood -lead concentration, which correlates with bad effects on the developing central nervous system in the young child. The Stern (1996) model was developed for non-residential land use scenarios; the exposed population of concern is adult males; and the selective critical effect is elevated blood pressure. Both models represent lead absorption and biokinetics as an intake blood -lead concentration slope factor(SF), which relates the incremental change in soil lead intake to an incremental change in the quasi-steady state PbB concentration. The Stern (1996) adult exposure model uses change in blood pressure in the adult male and resultant increase in incidence of hypertension in the exposed population as the sensitive endpoint.

The output of this model is a probability distribution reflecting combined variability and uncertainty associated with input variables. This is estimated using a one-dimensional Monte Carlo approach in which the combined variability and uncertainty associated with selected variables are represented with probability density function (PDF).

Stern's (1994) child model focuses on the de minimi increase in PbB concentration; therefore, the model does not account for a baseline PbB concentration. Use of this approach could result in cleanups that are over-or under-protective, depending on the specific baseline lead exposure of the receptor. Stern's (1996) adult model does have the baseline PbB concentration as an input parameter.

The Leggett(1993) model simulates the movement and deposition of lead in the body as exchanges between various tissue compartments and a central plasma compartment. Tissue compartments represented in the model include bound plasma, brain, extravascular fluid, gastrointestinal tract, kidney, liver, lung, other soft tissues, red blood cells, and skeletal tissues

(cortical and trabecular bone). Excretory routes represented in the model include feces, sweat, urine, and other routes (e.g., hair, nails, skin). Exchanges are described by age-specific transfer coefficients (analogous to first-order rate constants). The model is currently used by the International Commission on Radiological Protection to predict internal radiation doses of a variety of radionuclides that have biokinetics similar to those of calcium.

The Leggett model can track and record tissue lead accumulation over any selected age range. The model can also provide estimates of blood and tissue lead over a wide time frame that can vary from minutes to decades. The model is for all-ages model that can simulate lead accumulation in a variety of tissues over any selected age range for a wide range of lead intake patterns, including intakes that vary in intensity over time. The Leggett model works well over a wide variety of conditions as assessed by comparison between predicted and observed PbB concentrations and urinary or fecal excretion in adults and comparisons of predicted and observed post-mortem tissue lead concentrations. An additional strength of the model is that the source code for implementing the model can be easily executed on any computer with a FORTRAN compiler. The user has access to all variables and constants in the model. The model is very flexible in terms of the integration and communication intervals that can be selected by the user to accommodate complex time-varying exposures

One of the limitations of the Leggett model is the lack of an exposure model. In order to simulate an exposure scenario, the user must calculate and input the lead intakes that correspond to the exposure scenario. This approach may be too flexible for a regulatory model; guidance on calculating intakes from exposure concentrations would be needed. Other limitations to the model include the lack of statistical and graphics modules and the inability to start simulations from a baseline lead burden. The latter limitation requires the user to construct an intake scenario

to simulate the baseline condition. Also the model does not currently have a graphics or statistics output. Data files are generated that can be imported into spreadsheets for further tabular or graphical processing.

As part of the review, analysis of the performance of the models both qualitatively and quantitatively. Simulations were done (EPA 2001) under varying exposure assumptions to assess the sensitivity and performance of each model and to determine under which conditions the exposure assumptions break down. Each model was also compared using the same set of exposure conditions. As a result of this analysis, no model was judged to be a significant improvement over the other, hence various components from the models were determined to modify the lead model that can estimate the amount of lead in each compartment at equilibrium and to assess the behaviour of lead in each compartment as a result of assumed remedies with graphical output using Matlab.

## 2.1 Definition of differential equation

Many of the principles or laws underlying the behavior of the natural world are statements or relations involving rates at which things happen. When expressed in mathematical terms, these relations are equations and the rates are derivatives. Equations containing derivatives are called differential equations. A differential equation is therefore any equation containing a dependent variable together with its derivative.

## 2.2 Classification of differential equation

Just as biologists have a classification system for life, mathematicians also have a classification system for differential equations. On the basis of the classification, we can classify differential equation according to Type/category, Order, Homogeneity, Linearity and Degree.

### 2.2.1 Order

The order of a differential equation is the highest derivative that appears in the equation. Any ordinary differential equation can be written in the form:

$F\left(x, y, y', y'', \ldots, y^{(n)}\right) = 0$, by setting everything equal to zero.

The expressions $y', y'', y''', \ldots, y^n$ are often used to represent respectively, the 1st, 2nd, 3rd and $n^{th}$ derivatives of y with respect to the independent variable under consideration.

### 2.2.2 First Order Differential Equations

One of the classes of differential equations that is easily recognized and readily solved at least in principles is that of first-order linear differential equations. An equation is said to be first order linear, if it has the form.

$$y' + a(x)y = b(x) \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.1)$$

where both a(x) and b(x) are continuous functions. The "first-order" aspect is obvious: only first derivatives appear in the equation

## 2.3 Systems of Differential Equation.

A system such as (2.2) of n first-order equations is called a first-order ordinary system of differential equations.

$$\frac{dx_1}{dt} = g_1(t_1, x_1, x_2, \ldots, x_n)$$

$$\frac{dx_2}{dt} = g_2(t_1, x_1, x_2, \ldots, x_n) \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots(2.2)$$

$$\vdots \qquad\qquad \vdots \qquad \vdots$$

$$\frac{dx_n}{dt} = g_n(t_1, x_1, x_2, \ldots, x_n)$$

## 2.4 Linear systems

When each of the functions $g_1, g_2, \ldots, g_n$ in (2.2) is linear in the dependent variables, $x_1, x_2, \ldots, x_n$, we get the normal form of a first-order system of linear equations.

## 2.5 Homogeneity

We refer to a system of the form given in (2.3) below simply as a linear system. We assume that the coefficients $a_{ij}$ as well as the functions $f_i$ are continuous on a common interval I.When $f_i(t) = 0, i = 1, 2, 3, \ldots, n$ the linear system (2.3) is said to be homogeneous; otherwise, it is nonhomogeneous.

$$\frac{dx_1}{dt} = a_{11}(t)x_1 + a_{12}(t)x_2 + \cdots + a_{1n}(t)x_n + f_1(t)$$

$$\frac{dx_2}{dt} = a_{21}(t)x_1 + a_{22}(t)x_2 + \cdots + a_{2n}(t)x_n + f_2(t) \qquad \ldots\ldots\ldots\ldots..(2.3)$$

$$\vdots \qquad\qquad\qquad\qquad \vdots$$

$$\frac{dx_n}{dt} = a_{n1}(t)x_1 + a_{n2}(t)x_2 + \cdots + a_{nn}(t)x_n + f_n(t)$$

## 2.6 Theorems

### 2.6.1 Existence and uniqueness for linear systems

Let the vector $x\,(t)$ with the $n$ elements $x_i(t), (i = 1, 2, \ldots, n)$ be the solution of the nonhomogeneous variable coefficient system of first order linear differential equations

$$x'(t) = A(t)x(t) + b(t)$$

where the functions $a_{ij}\,(t), (i, j = 1, 2, \ldots, n)$ forming the elements of $\boldsymbol{A}(t)$ and the elements $f_i\,(t), (i = 1, 2, \ldots, n)$ Forming the elements of the vector $\boldsymbol{b}(t)$ are continuous functions in some interval $a < t < b$. Furthermore, let the elements of $\boldsymbol{x}(t)$ satisfy the initial conditions $x_i\,(t_i) = k_i\,(i = 1, 2, \ldots, n)$, where the $k_i$ are given constants and $t_0$ is any point such that $a < t_0 < b$. Then the solution of the initial value problem exists and is unique for all $t$ such that $a < t < b$.

### 2.6.2 Principle of superposition

Let $x_1, x_2, \ldots, x_n$ be $n$ solutions of the homogeneous linear equation $\frac{dx}{dt} = P(t)x$ on the open interval *I*. If $c_1, c_2, \ldots, c_n$ are constants, then the linear combination

$x(t) = c_1x_1(t) + c_2x_2(t) + \cdots + c_nx_n(t)$ is also a solution of the homogenous linear equation.

### 2.6.3 Gershgorin's circle theorem

Let $A$ be a complex $n \times n$ matrix , with $a_{ij}$ for $i, j \in \{1, 2, \ldots, .n\}$ Let $R_i = \sum_{j \neq i}^{n} |a_{ij}|$ be the sum of the absolute values of the non-diagonal entries in the $i^{th}$ row. Let $D(a_{ii}, R_i)$ be the closed disc centered at $a_{ii}$ with radius $R_i$. Such a disc is called Gershgorin's disc.

The theorem states that, every eigenvalue of $A$ lies within at least one of the Gershgorin's disc $D(a_{ii}, R_i)$.

## 2.7 Methods of solving systems of differential equations

There are different methods of solving systems (homogenous/nonhomogeneous) of differential equations and some of these methods are: Variation of parameters, Method of undetermined, coefficients Numerical methods, Eigen value approach.

However, for the sake of our study, we shall talk briefly on the following topics:

i. Eigen value approach.

ii. Variation of parameters.

### 2.7.1 Eigenvalue method (homogenous system)

In outline, this method for solving the $n\ x\ n$ homogeneous constant-coefficient system

$x' = Ax$ proceeds as follows:

1. We first solve the characteristic equation (A-$\boldsymbol{\lambda}$I) for the eigenvalues $\boldsymbol{\lambda}_1, \boldsymbol{\lambda}_2, \ldots, \boldsymbol{\lambda}_n$ of the matrix A.

2. Next we attempt to find *n* linearly independent eigenvectors $v_1, v_2, \ldots, v_n$ associated with these eigenvalues.

3. Step 2 is not always possible, but when it is, we get n linearly independent solutions

$$x_1(t) = v_1 e^{\lambda 1_t}, \qquad x_2(t) = v_2 e^{\lambda 2_t}, \ldots, \qquad x_n(t) = v_n e^{\lambda n_t}$$

In this case the general solution of x' = Ax is a linear combination

$$x(t) = c_1 x_1(t) + c_2 x_2(t) + \cdots + c_n x_n(t)$$

of these n solutions.

**2.7.2 Variation of parameters (nonhomogeneous system)**

We ask whether it is possible to replace the matrix of constants **C** in $X = \Phi(t)C$ by a column matrix of functions

$$U(t) = \begin{pmatrix} U_1(t) \\ U_2(t) \\ \vdots \\ U_n(t) \end{pmatrix}, \quad \text{so } X_P = \Phi(t)U(t)$$

is a particular solution of the nonhomogeneous system

$$x' = Ax + F(t)$$

By the Product Rule the derivative of the expression in the $X_p$ equation is

$$x'_p = \Phi(t)U'(t) + \Phi'(t)U(t)$$

Note that the order of the products in the above equation is very important. Since U(t) is a column matrix, the products $U'(t)\Phi(t)\ and\ U(t)\Phi'(t)$ are not defined. Substituting gives

$$\Phi(t)U'(t) + \Phi'(t)U(t) = A\Phi(t)U(t) + F(t)$$

Now replacing $\Phi'(t)\ with\ A\Phi(t), we\ get$

$$\Phi(t)U'(t) + A\Phi(t)U(t) = A\Phi(t)U(t) + F(t)$$

$$\Phi(t)U'(t) = F(t)$$

Multiplying both sides by $\Phi^{-1}(t)$ gives

$U'(t) = \Phi^{-1}(t)F(t)$, and so $U(t) = \int \Phi^{-1}(t)F(t)dt.$

Since $X_p = \Phi(t)U(t)$, we conclude that, a particular solution of the equation is

$$X_p = \Phi(t) \int \Phi^{-1}(t)F(t)dt. \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.4)$$

Therefore, the general solution becomes

$$X = X_c + X_p$$

$X = \Phi(t)C + \Phi(t) \int \Phi^{-1}(t)F(t)dt.$ ……(2.5)

In order to proceed and simplify this solution further, let us review our exponential matrices.

## 2.8 Exponential Matrices

We now discuss the possibility of constructing a fundamental matrix for the constant coefficient linear system $x' = Ax$ directly from the coefficient matrix $A$-that is, without first applying the methods of earlier sections to find a linearly independent set of solution vectors.

We have seen that exponential functions play a central role in the solution of linear differential equations and systems, ranging from the scalar equation $x' = kx$ with solution $x(t) = x_0e^{kt}$ to the vector solution $x(t) = ve^{\lambda t}$ of the linear system $x' = Ax$ whose coefficient matrix $A$ has eigenvalue $\mu$ with associated eigenvector $v$.We now define exponentials of matrices in such a way that $X(t) = e^{At}$ is a matrix solution of the matrix differential equation $X' = AX$ with n x n coefficient matrix A-in analogy with the fact that the ordinary exponential function $x(t) = e^{at}$ is a scalar solution of the first-order differential equation $x' = ax$.

The exponential $e^z$ of the complex number z may be defined by means of the exponential series

$$e^z = 1 + z + \frac{z^2}{2!} + \frac{z^3}{3!} + \ldots + \frac{z^n}{n!} + \ldots \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.6)$$

Similarly, if A is an n x n matrix, then the exponential matrix $e^A$ is the n x n matrix defined by the series

$$e^A = I + A + \frac{A^2}{2!} + \frac{A^3}{3!} + \ldots + \frac{A^n}{n!} + \ldots \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.7)$$

where $\boldsymbol{I}$ is the identity matrix. The meaning of the infinite series on the right hand side

is given by

$$\sum_{n=0}^{\infty} \frac{A^n}{n!} = \lim_{k\to\infty} \left( \sum_{n=0}^{k} \frac{A^n}{n!} \right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.8)$$

where $A^0 = I, A^1 = A, A^2 = AA, A^3 = AA^2$ and so on; inductively, $A^{n+1} = AA^n$ if $n \geq 0$

It can be shown that the limit in (2.8) exists for every $n\,x\,n$ square matrix A. That is, the exponential matrix $e^A$ is defined by (2.7) for every square matrix A.

In particular, the matrix $e^A$ is nonsingular for every $n\ x\ n$ matrix $A$. It follows from elementary linear algebra that the column vectors of $e^A$ are always linearly independent.

If t is a scalar variable, then substitution of $At$ for $A$ in Eq. (2.7) gives

$$e^{At} = I + At + A^2\frac{t^2}{2!} + A^3\frac{t^3}{3!} + \ldots + A^n\frac{t^n}{n!} + \ldots \qquad \ldots\ldots\ldots\ldots\ldots (2.9)$$

## 2.9 Matrix Exponential Solutions

It happens that term-by-term differentiation of the series in (2.9) is valid, with the Result

$$\frac{d}{dt}(e^{At}) = A + A^2t + A^3\frac{t^2}{2!} + \ldots = A(I + At + A^2\frac{t^2}{2!} + \ldots) \qquad \ldots\ldots\ldots (2.10)$$

Hence, we have $\frac{d}{dt}(e^{At}) = Ae^{At}$. In analogy to the formula $D_t(e^{kt}) = ke^{kt}$ from elementary calculus. Thus the matrix-valued function

$$X(t) = e^{At}$$

satisfies the matrix differential equation

$$X' = AX$$

Because the matrix $e^{At}$is nonsingular, it follows that the matrix exponential $e^{At}$ is a fundamental matrix for the linear system $X' = AX$ . In particular, it is the fundamental matrix $X(t)$ such that $X(0) = I$.

## 2.10 Theorem (Matrix Exponential Solutions)

If $A$ is an $n\ x\ n$ matrix, then the solution of the initial value problem

$X' = AX$ , $X(0) = X_0$ is given by $X(t) = X_0e^{At}$ and this solution is unique.

Now equation (2.4) and the theorem (2.10) hold for any fundamental matrix $\Phi(t)$ of the homo-geneous system $X' = AX$. we can use for $\Phi(t)$ the exponential matrix $e^{At}$ that is, the particular fundamental matrix such that $\Phi(0) = e^{A(0)} = I$ Then, because $(e^{At})^{-1} = e^{-At}$ substitution of $\Phi(t) = e^{At}$ in yields the particular solution

$$X_p = e^{At} \int e^{-At} F(t)dt \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.11)$$

Therefore the general solution of the initial value problem $X' = AX + F(t)$, $X(0) = X_0$ can written as

$$X = X_c + X_p$$

$$X = X_0 e^{At} + e^{At} \int e^{-At} F(t)dt \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2.12)$$

# CHAPTER THREE

# METHODOLOGY

## 3.1 Introduction

The human body is divided into three compartments, the Blood stream, the Tissue and the Bone. The lead gets into the human system through different paths and transfer from one compartment to another through several blood vessels. Lead is taken from outside by two ways via the Lungs (Air) and the Digestive tract (Diet) and these are the main sources of lead intake. Lead can also get into the system through the Digestive tract by way of tissue (saliva, gastric secretion, bile, etc.).

Some quantity of lead also escapes the human system through different means. Lead escapes the body through normal breathing (Lungs) and bowel movements (digestive tract). Lead can also escape from the body by way of the blood (urine) and the tissue (Hair, Nails, Sweat etc.).

The human body functions well because there is co-ordination among the individual parts and consequently, exchange of quantity of lead takes place. There is an exchange of lead between the tissue, the blood stream and the bones.

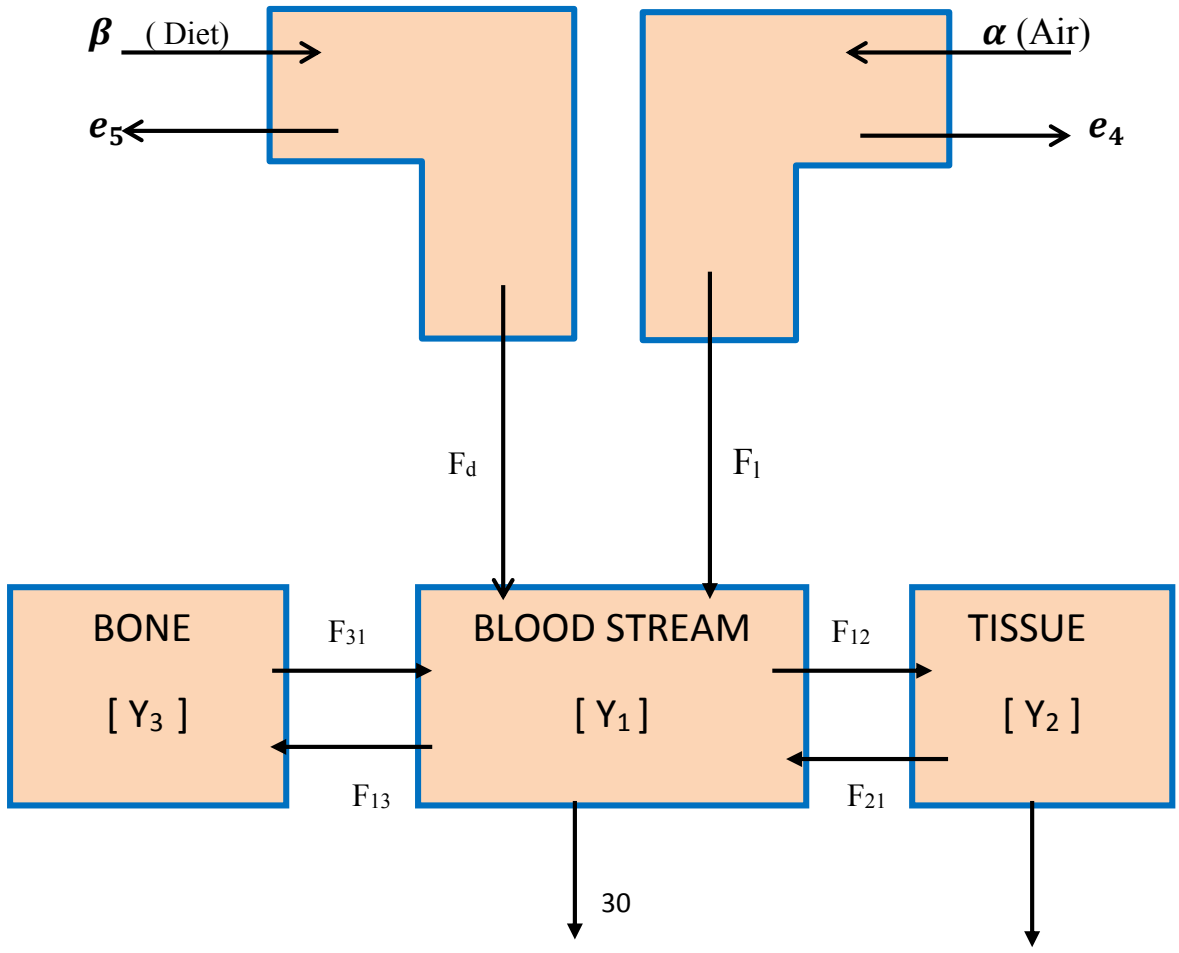
## 3.2 Model Development

### 3.2.1 Model Assumptions

The rate at which lead transfers from the lungs to the blood stream is proportional to the rate at which lead enters the lungs. The rate at which lead transfers from the digestive tract to the blood stream is proportional to the rate at which lead enters the digestive tract.

Also the rate at which lead transfers from the blood compartment to the tissue compartment is proportional to the amount of lead in the blood compartment. The rate at which lead transfers from the tissue compartment to the blood compartment is proportional to the amount of lead in the tissue compartment. The rate at which lead transfers from the blood compartment to the bone compartment is proportional to the amount of lead in the blood compartment. The rate at which lead transfers from the bone compartment to the blood compartment is proportional to the amount of lead in the bone compartment. The rate at which lead transfers from the tissue compartment to the digestive tract is proportional to the amount of lead in the tissue compartment. Finally it is important to note that lead transfer is measured in micrograms per day (µg / day).

### 3.2.2 The Schematic of Lead Transfer



$e_1$ $e_2$

(urine, etc.) ( faeces, hair, sweat, nails etc.)

### 3.2.3The Model

Assume that all lead transfer is measured in micrograms per day (µg / day), we now model the exchange of lead using first order systems of Differential equations as follows:

let $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ be the rate at which lead enters the Lungs and the Digestive tract respectively. Let $\boldsymbol{F_{25}}$be the rate at which lead enters the digestive tract by way of tissue (saliva, Gastric secretion, bile, etc.). Let $\boldsymbol{F_l}$ be the rate at which lead enters the blood stream through the lungs and $\boldsymbol{F_d}$ be the rate at which lead enters the blood stream through the digestive tract. Hence the rate $\boldsymbol{F_{ld}}$ at which lead enters the blood stream via the lungs and the digestive tract is $\boldsymbol{F_l + F_d}$

Also let $\boldsymbol{e_4}$ be the rate at which lead escape the lungs through the normal breathing, and $\boldsymbol{e_5}$ be the rate at which lead escape the Digestive tract through bowel movements. Also let $\boldsymbol{e_1}$ be the rate at which lead escape from the blood through urine and let $\boldsymbol{e_2}$ be the rate at which lead escape from the tissue through Hair, nails, sweat etc.

Let $\boldsymbol{F_{12}}$ be the rate at which lead enters the tissue from the blood stream and $\boldsymbol{F_{21}}$ be the rate at which lead comes back to the blood stream from the tissue compartment. Also let $\boldsymbol{F_{13}}$ be the rate at which lead enters the Bones from the blood and $\boldsymbol{F_{31}}$ be rate at which lead comes back to the blood from the bone compartment.

Using the rate equations

The rate $\boldsymbol{F_l}$ at which lead transfer from the lungs to the blood is equal to the rate at which the lungs absorb the lead

$$F_l = \alpha - e_4 \qquad \ldots\ldots\ldots\ldots\ldots \quad (3.1)$$

We assume that this rate is proportional to the rate at which lead enters the lungs, where $p$ is a constant of proportionality. Thus

$$F_l = \alpha - e_4 \ = p\alpha \qquad where\ \ 0 < p < 1 \qquad \ldots\ldots\ldots\ldots\ldots \quad (3.2)$$

Also the rate $F_d$ at which lead transfer from the digestive tract to the blood stream equal to the rate at which the digestive tract absorb the lead. Here, the digestive tract absorb from two sources, the tissue and the diet. Assume that this rate is proportional to the rate at which lead enters the digestive tract, where $q$ is a constant of proportionality. Thus

$$F_d = q(\beta + F_{25}) \qquad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3.3)$$

Therefore the rate at which lead enters the blood stream from the digestive tract and the lungs is equals the rate at which lead enters the blood from the digestive tract plus the rate at which lead enters the blood from the lungs. Hence,

$$F_{dl} = F_d + F_l = q(\beta + F_{25}) \ + p\alpha \qquad \ldots\ldots\ldots\ldots\ldots (3.4)$$

If we let $Y_1(t)$, $Y_2(t)$, $Y_3(t)$ represent the amount of lead in the blood, tissue and the bone respectively. Therefore, $Y_1'(t)$, represent the rate at which lead enters and escape the blood compartment. This is equal to the rate at which lead comes into the blood compartment minus the rate at which lead escape the compartment. $Y_2'(t)$, represent the rate at which lead enters and escape the tissue compartment. This is equal to the rate at which lead comes into the tissue compartment minus the rate at which lead escape the compartment. Also, $Y_3'(t)$, represent the rate at which lead enters and escape the bone compartment. This is equal to the rate at which lead comes into the bone compartment minus the rate at which lead escape the compartment. These

statements can be express mathematically to give systems of three differential equations as follows.

$$Y_1'(t) = F_{21} - F_{12} + F_{31} - F_{13} + F_{dl} - e_1$$

$$Y_2'(t) = F_{12} - F_{21} - F_{25} - e_2 \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ (3.5)$$

$$Y_3'(t) = F_{13} - F_{31}$$

Let us also assume that the lead transfer $F_{12}$ from the blood compartment to the tissue compartment is proportional to the amount of lead in the blood compartment. The lead transfer $F_{21}$ from the tissue compartment to the blood compartment is proportional to the amount of lead in the tissue compartment. The lead transfer $F_{13}$ from the blood compartment to the bone compartment is proportional to the amount of lead in the blood compartment. The lead transfer $F_{31}$ from the bone compartment to the blood compartment is proportional to the amount of lead in the bone compartment. The lead transfer $F_{25}$ from the tissue compartment to the digestive tract is proportional to the amount of lead in the tissue compartment. Thus

$$F_{12} = a_{12}Y_1 \qquad F_{21} = a_{21}Y_2$$

$$F_{13} = a_{13}Y_1 \qquad F_{31} = a_{31}Y_3 \qquad \ldots\ldots\ldots\ldots\ldots(3.6)$$

$$F_{25} = a_{25}Y_2 \qquad e_1 = bY_1$$

$$e_2 = cY_2$$

Where $a_{ij}$ , $b$, $and$ $c$ are positive constants.

Substituting equation (3.4) and (3.6) into equation (3.5), we have the following:

$$Y_1'(t) = a_{21}Y_2 - a_{12}Y_1 + a_{31}Y_3 - a_{13}Y_1 + p\alpha + q(\beta + a_{25}Y_2) - bY_1$$

$$Y_2'(t) = a_{12}Y_1 - a_{21}Y_2 - a_{25}Y_2 - cY_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.7)$$

$$Y_3'(t) = a_{13}Y_1 - a_{31}Y_3$$

$$Y_1'(t) = -(a_{12} + a_{13} + b)Y_1 + (a_{21} + qa_{25})Y_2 + (a_{31})Y_3 + p\alpha + q\beta$$

$$Y_2'(t) = a_{12}Y_1 - (a_{21} + a_{25} + c)Y_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.8)$$

$$Y_3'(t) = a_{13}Y_1 - a_{31}Y_3$$

Hence by combining coefficients the equation can be simplified as follows;

$$Y_1'(t) = -A_{11}Y_1 + A_{12}Y_2 + A_{13}Y_3 + N$$

$$Y_2'(t) = A_{21}Y_1 - A_{22}Y_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.9)$$

$$Y_3'(t) = A_{31}Y_1 - A_{33}Y_3$$

Therefore, we have three linear non-homogeneous differential equations with **N** as the non-homogeneous part and it is given by

$$N = p\alpha + q\beta \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.10)$$

$$\begin{pmatrix} Y_1'(t) \\ Y_2'(t) \\ Y_3'(t) \end{pmatrix} = \begin{pmatrix} -A_{11} & A_{12} & A_{13} \\ A_{21} & -A_{22} & 0 \\ A_{31} & 0 & -A_{33} \end{pmatrix} \begin{pmatrix} Y_1 \\ Y_2 \\ Y_3 \end{pmatrix} + \begin{pmatrix} N \\ 0 \\ 0 \end{pmatrix}$$

$$Y' = AY + F \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.11)$$

## 3.3 Stability of Critical points

A critical point $x=c$ of a differential equation is said to be stable provided that, if the initial value $x_0$ is sufficiently close to $c$, then $x(t)$ remains close to $c$, for all $t>0$. More precisely, the critical point $c$ is stable if, for each $\varepsilon>0$, there exist $\delta>0$, such that,

$$|x_0 - c| < \delta \quad implies, \quad |x(t) - c| < \varepsilon.$$

The critical point $x = c$ is said to be unstable if it is not stable.

### 3.3.1 Types of Critical points

At this point, we try to discuss some of the types of critical/equilibrium points that is used to determine the stability of a system of differential equations. We would like to use the model in this study to explain some of these critical points. We must also remember that, the type of critical point is determined by the Eigen values obtained from the system of equations. From the model:

i. If the Eigen values are all positive, real and distinct, the equilibrium/critical point is unstable source.

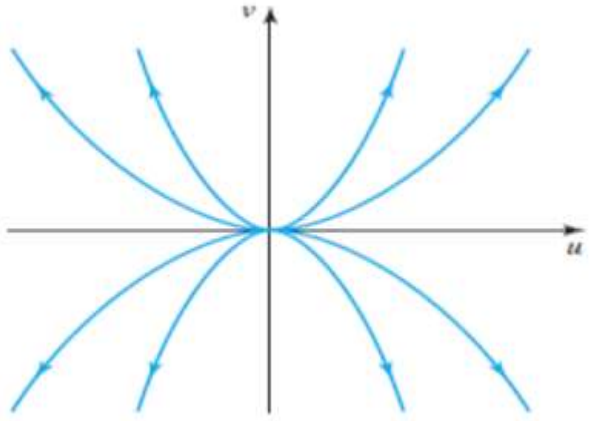



Fig 3.1 Phase portrait of unstable source

ii. If the Eigen values are all negative, real and distinct, equilibrium point is a stable sink.

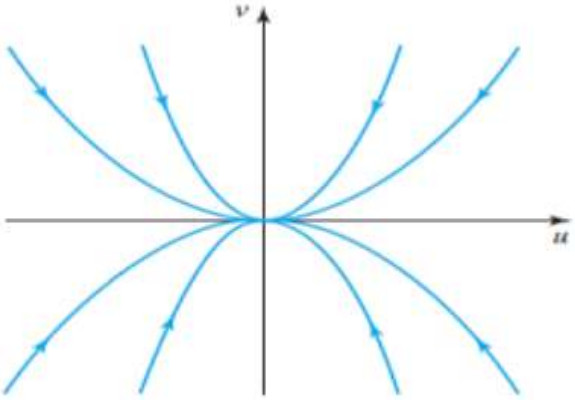



Fig3.2 Phase portrait of a stable sink

iii. If the Eigen values are real, distinct and have alternating signs, equilibrium point is unstable saddle.

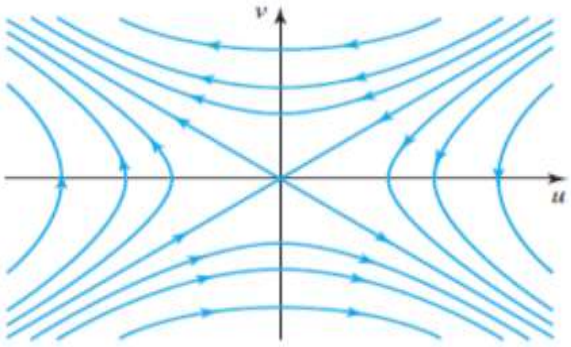



Fig3.3Phase portrait of unstable saddle

iv. If the Eigen values are all positive, real and equal (repeated), equilibrium point is said to be unstable star source.

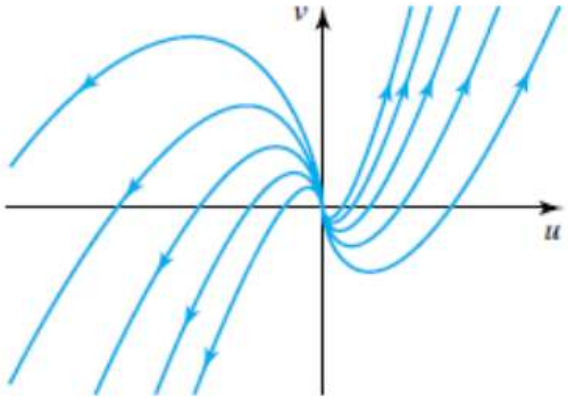



Fig3.4 Phase portrait of unstable star source

v. If the Eigen values are all negative, real and equal, equilibrium point is said to be a stable star sink.

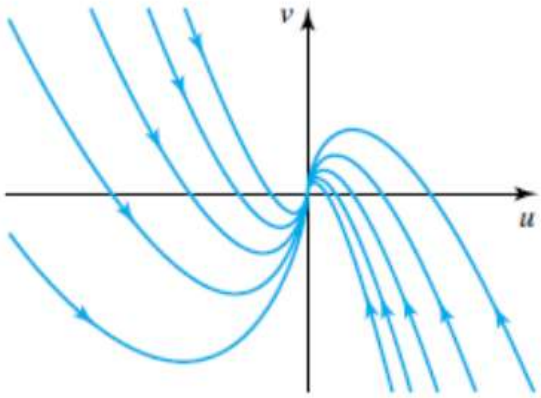



Fig3.5 Phase portrait of stable star sink

vi. If the Eigen values are complex and purely imaginary, equilibrium point is a stable center.

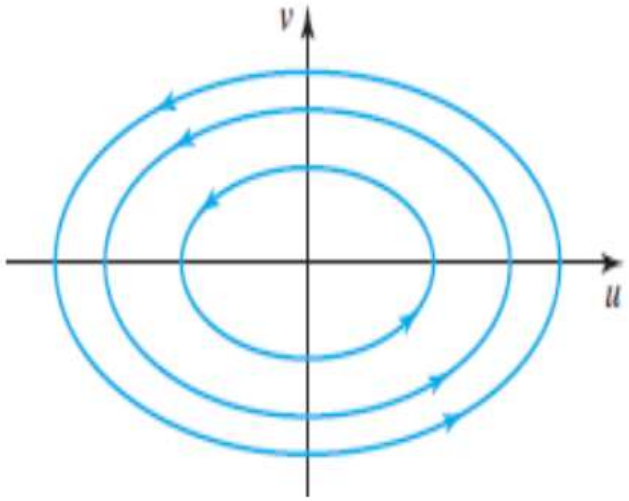



Fig3.6 Phase portrait of stable center

vii. If the Eigen values are complex with a positive real part, equilibrium point is unstable spiral source.

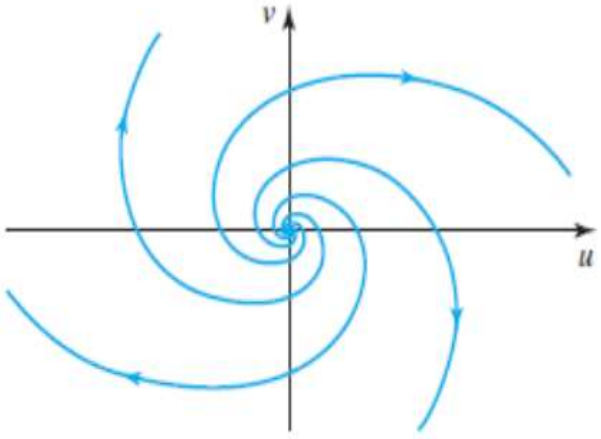



Fig3.7 Phase portrait of unstable spiral source

viii. If the Eigen values are complex with a negative real part, equilibrium point is a stable spiral sink.

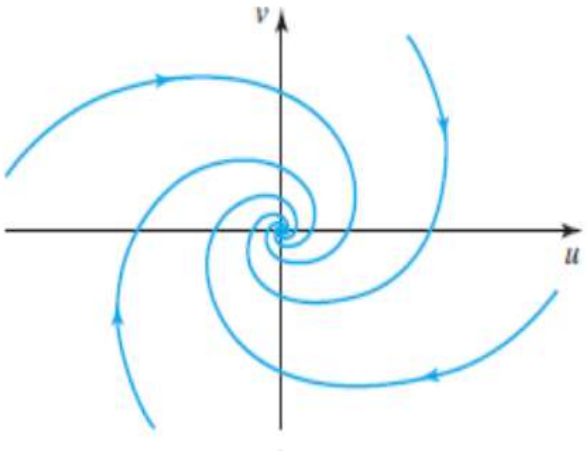



Fig3.8 Phase portrait of a stable spiral sink

## 3.4 Solution by Variation of Parameters

The system (3.11)

$Y' = AY + F \quad , \; Y(0) = Y_0$

Where $Y$ is the vector of $Ys$ and $F$ is the nonhomogeneous part, thus

$F = \begin{pmatrix} N \\ 0 \\ 0 \end{pmatrix}$ and $A$ is the 3×3 matrix of the homogeneous part thus;

$$A = \begin{pmatrix} -A_{11} & A_{12} & A_{13} \\ A_{21} & -A_{22} & 0 \\ A_{31} & 0 & -A_{33} \end{pmatrix}$$

Hence from chapter two (2), The General Solution of the system (3.11) is given by

$Y = Y_c + Y_p$ where $Y_c$ is the complementary solution of the homogeneous part and $Y_p$ is the particular solution of the nonhomogeneous part. Hence using variation of parameters the solution is given by;

$$Y = e^{At}Y_0 + e^{At}\int_0^t e^{-As}Fds \qquad \text{……..(3.12)}$$

Suppose that the intake of lead N is a constant. This is a reasonable assumption if the environmental lead remains constant. Then F is also a constant vector and we may carry out the integration as follows;

$$Y = e^{At}Y_0 + \int_0^t e^{A(t-s)}Fds$$

$$Y = e^{At}Y_0 + F\left[-A^{-1}e^{A(t-s)}\right]_0^t$$

$$Y = e^{At}Y_0 - A^{-1}F\left[e^{A(t-s)}\right]_0^t$$

$$Y = e^{At}Y_0 - A^{-1}F[I - e^{At}]$$

$$Y = e^{At}Y_0 - A^{-1}F + A^{-1}Fe^{At}$$

$$Y = [Y_0 + A^{-1}F]e^{At} - A^{-1}F \qquad \text{……..(3.13)}$$

Hence (3.13) is the solution of the system provided $A^{-1}$ exist ( i.e A is nonsingular). We can obtain the solution provided that the exponential $e^{At}$ is computable.

## 3.5 The Long term Prediction

The long-term behavior of the solution is predicted by eigenvalues of the matrix $A$. Since the diagonal entries of $A$ are all negative, by Gershgorian circle theorem, the eigenvalues of $A$ are negative or zero real parts.

If the eigenvalues tends out to be strictly negative, then the exponential $e^{At}$ tends to the zero matrix as $t \to \infty$, as a result the long term solution is given by;

$Y \to -A^{-1}F$ as $t \to \infty$. ……..(3.14)

# CHAPTER FOUR

# ANALYSIS

## 4.1 The Subject Data

To analyze the behavior of lead transfer in the body, we need to estimate the values of the constants $\boldsymbol{A_{ij's}}$ and $\boldsymbol{N}$ using a real life situation.

The following data was gotten from a Journal of mathematical Biology in 1979. The Author used a healthy person, 53 years old, male, weighing 70kg, smoking eight cigarettes per day. The person lived in the southern California. After 104 days the subject studied was considered to be in a stable state with respect to lead. The data is as follows;

| Variable | Description | Value |
|---|---|---|
| $Y_1$ | Amount of lead in the blood stream | $1800\mu g$ |
| $Y_2$ | Amount of lead in the tissue | $700\mu g$ |
| $Y_3$ | Amount of lead in the bone | $200000\mu g$ |
| $F_{12}$ | Rate at which lead transfer from the blood to the tissue | $20\,\mu g/d$ |
| $F_{21}$ | Rate at which lead transfer from the tissue to the blood | $8\,\mu g/d$ |
| $F_{13}$ | Rate at which lead transfer from the blood to the bone | $7\,\mu g/d$ |
| $F_{31}$ | Rate at which lead transfer from the bone to the blood | $7\,\mu g/d$ |
| $F_l$ | Rate at which lead transfer from the lungs to the blood | $17\,\mu g/d$ |
| $F_d$ | Rate at which lead transfer from the digestive tract to the blood | $33\,\mu g/d$ |
| $F_{25}$ | Rate at which lead enters the digestive tract through the tissue | $8\,\mu g/d$ |
| $e_1$ | Rate at which lead escape from the blood via urine | $38\,\mu g/d$ |

| | | |
|---|---|---|
| $e_2$ | Rate at which lead escape from the tissue via hair, sweat, nails | $4\,\mu g/d$ |
| $e_4$ | Rate at which lead escape from the lungs via normal breathing | $32\,\mu g/d$ |
| $e_5$ | Rate at which lead escape from the digestive tract via bowel movements | $38\,\mu g/d$ |
| $\alpha$ | Rate at which lead enters the lungs via breathing | $49\,\mu g/d$ |
| $\beta$ | Rate at which lead enters digestive tract via diet | $367\,\mu g/d$ |

Fig 4.1: Data from the journal of mathematical biology,

Using the data in the table above, we calculate the for the constants as follows;

Putting $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ into equation (3.10) we have;

$$\boldsymbol{N = 49p + 367q} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (\mathbf{4.1})$$

From equation (3.2) and equation (3.3)

$$\boldsymbol{F_l = \alpha - e_4 = 49p} \quad , \qquad \boldsymbol{17 = 49p} \quad , \quad \boldsymbol{p = \frac{17}{49}}$$

$$\boldsymbol{F_d = q(\beta + F_{25})} \, , \quad \boldsymbol{33 = q(367 + 8)} \quad , \quad \boldsymbol{q = \frac{11}{125}}$$

Hence substituting **p** and **q** into equation (4.1);

$$\boldsymbol{N = 49\left(\frac{17}{49}\right) + 367\left(\frac{11}{125}\right) = \frac{6162}{125}}$$

Also putting$\boldsymbol{Y_1}$ $\boldsymbol{Y_2, Y_3}$ , $\boldsymbol{e_1}$ and $\boldsymbol{e_2}$ into equation (3.6);

$$\boldsymbol{F_{12} = a_{12} Y_1} \qquad \boldsymbol{F_{21} = a_{21} Y_2}$$

$20 = a_{12}(1800)$ $\qquad$ $8 = a_{21}(700)$

$$\boldsymbol{a_{12} = \frac{1}{90}} \qquad \boldsymbol{a_{21} = \frac{2}{175}}$$

$$\boldsymbol{F_{13} = a_{13} Y_1} \qquad \boldsymbol{F_{31} = a_{31} Y_3}$$

$7 = a_{13}(1800)$ $7 = a_{31}(200000)$

$\boldsymbol{a_{13} = \frac{7}{1800}}$ $\boldsymbol{a_{31} = \frac{7}{200000}}$

$\boldsymbol{F_{25} = a_{25}Y_2}$ $\boldsymbol{e_1 = bY_1}$

$\boldsymbol{8 = a_{25}(700)}$ $\boldsymbol{38 = b(1800)}$

$\boldsymbol{a_{25} = \frac{2}{175}}$ $\boldsymbol{b = \frac{19}{900}}$

$\boldsymbol{e_2 = cY_2}$ , $\boldsymbol{4 = c(700)}$ $\boldsymbol{c = \frac{1}{175}}$

Also from equation (3.9)

$\boldsymbol{A_{11} = -(a_{12} + a_{13} + b)}$

$\boldsymbol{A_{11} = -\left(\frac{1}{90} + \frac{7}{1800} + \frac{19}{900}\right) = -\frac{13}{360}}$

$\boldsymbol{A_{12} = (a_{21} + qa_{25})}$

$\boldsymbol{A_{12} = \frac{2}{175} + \left(\frac{11}{125}\right)\left(\frac{2}{175}\right) = \frac{272}{21875}}$

$\boldsymbol{A_{13} = a_{31} = \frac{7}{200000}}$

$\boldsymbol{A_{21} = a_{12} = \frac{1}{90}}$

$\boldsymbol{A_{22} = -(a_{21} + a_{25} + c)}$

$\boldsymbol{A_{22} = -\left(\frac{2}{175} + \frac{2}{175} + \frac{1}{175}\right) = -\frac{1}{35}}$

$\boldsymbol{A_{31} = a_{13} = \frac{7}{1800}}$

$A_{33} = -a_{31} = -\frac{7}{200000}$

Hence substituting all the values into the system, equation (3.9) we have;

$$\boldsymbol{Y_1'(t) = -\frac{13}{360}Y_1 + \frac{272}{21875}Y_2 + \frac{7}{200000}Y_3 + \frac{6162}{125}}$$

$$\boldsymbol{Y_2'(t) = \frac{1}{90}Y_1 - \frac{1}{35}Y_2} \qquad \boldsymbol{\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4.2)}$$

$$\boldsymbol{Y_3'(t) = \frac{7}{1800}Y_1 - \frac{7}{200000}Y_3}$$

## 4.2 Stability Analysis

By the Gershgorin circle theorem, the system is stable and behaves as a damped oscillator because of the negativity nature of the eigenvalues. This is shown by the plot of response with time and the situation would be sinusoidal with ever-decreasing amplitude.

### 4.2.1 Eigenvalues and eigenvectors of the system

Using matlab we compute the eigenvalues and the eigenvectors as follows

```
>> A=[-13/360 272/21875 7/200000;1/90 -1/35 0.00;(7/1800) 0.00 (-7/200000)];

>> [evec, eval] = eig(A)
```

```
evec =

  -0.8212    0.6065    0.0011

   0.5662    0.7862    0.0004

   0.0715   -0.1181    1.0000
```

eval =

-0.0447 0 0

0 -0.0200 0

0 0 -0.0000

Hence the eigenvalues the system are $\lambda_1 = -0.0447,\ \lambda_2 = -0.0200,\ \lambda_3 = -0.0000$ and their corresponding eigenvectors are $v_1 = \begin{pmatrix} -0.8212 \\ 0.5662 \\ 0.0715 \end{pmatrix}, v_2 = \begin{pmatrix} 0.6065 \\ 0.7862 \\ -0.118 \end{pmatrix}$ $v_3 = \begin{pmatrix} 0.0011 \\ 0.0004 \\ 1.000 \end{pmatrix}$ . The eigenvalues gives a confirmation that our system is stable.

### 4.2.2 Phase portrait

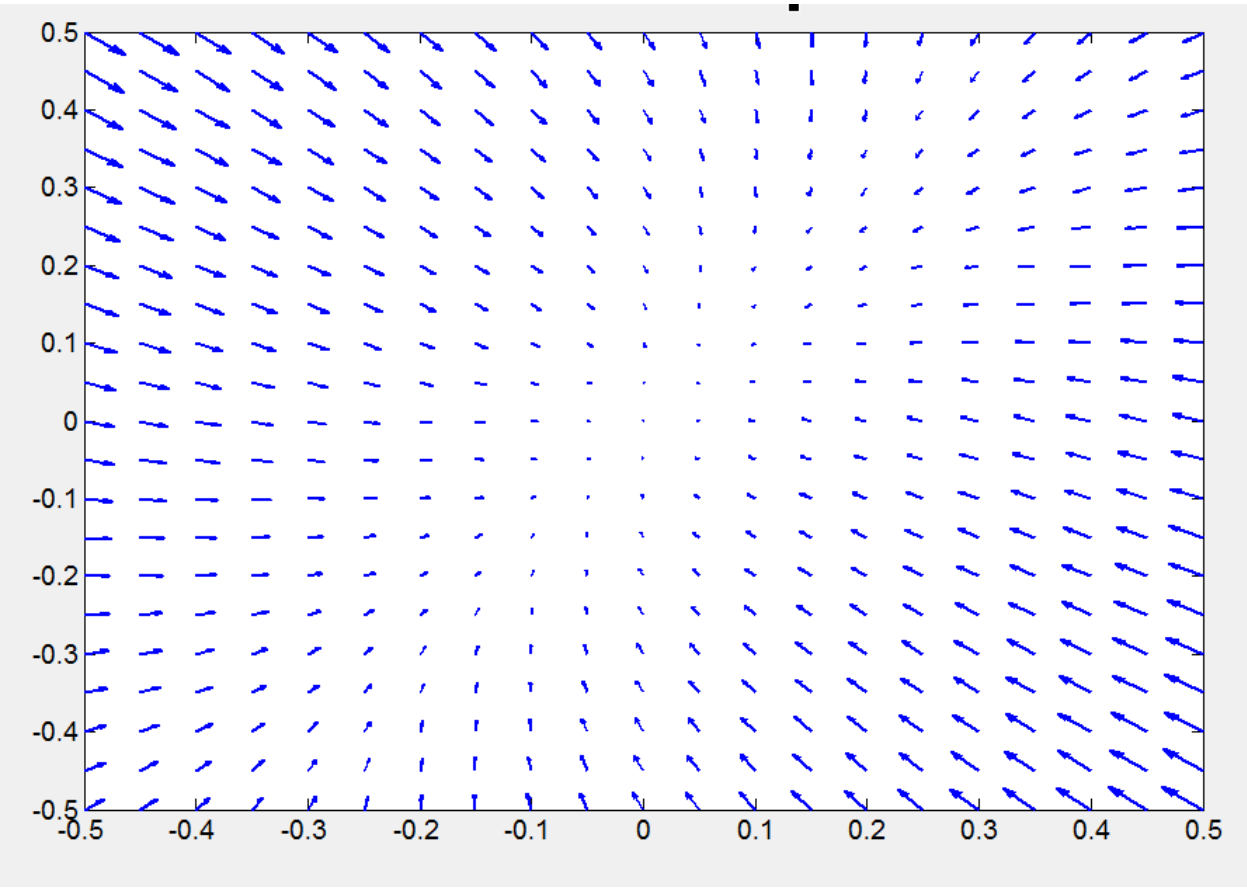



Fig. 4.1 Phase portrait of stable point

## 4.3 Long term solution (prediction)

The solution of our system is of the form $Y(t) = Y_c(t) + Y_p(t)$ this comprises of the transient state solution ( $Y_c(t)$) that depends only on the initial conditions, it dies out with time leaving the steady state solution ( $Y_p(t)$) resulting from the external deriving force $F$.

$Y(t) = [Y_0 + A^{-1}F]e^{At} - A^{-1}F$

Therefore, the solution is given by

$Y(t) \to -A^{-1}F \; as \; t \to \infty$

We then compute the solution with matlab as follows

>> A=[-13/360 272/21875 7/200000;1/90 -1/35 0.00;(7/1800) 0.00 (-7/200000)];

>> F = [6162/125;0;0];

>> Y= -inv(A)*F

Y = (1800, 700, 200000)

Hence the amount of lead in the Blood is $1800\ \mu g$, in the Tissue is $700\mu g$ and in the Bone is $200000\mu g$ in the long run.

## 4.4 Graphical analysis (plotting the system)

Using the first order system of differential equation above, several cases are applied. The equation is used to plot a graph in Matlab. We can observe from the figure (Fig.4.2) that, the lead in the blood and tissue quickly goes to equilibrium levels. But the lead in the bones continues increasing. This is because the coefficient of $Y_3$ is very small. This means that the amount of lead that transfers back from the bones to the blood is so small that the lead accumulates in the bones.

Even after 1000 days, the lead in the bones is an enormous quantity compared with other two compartments (Fig. 4.3).

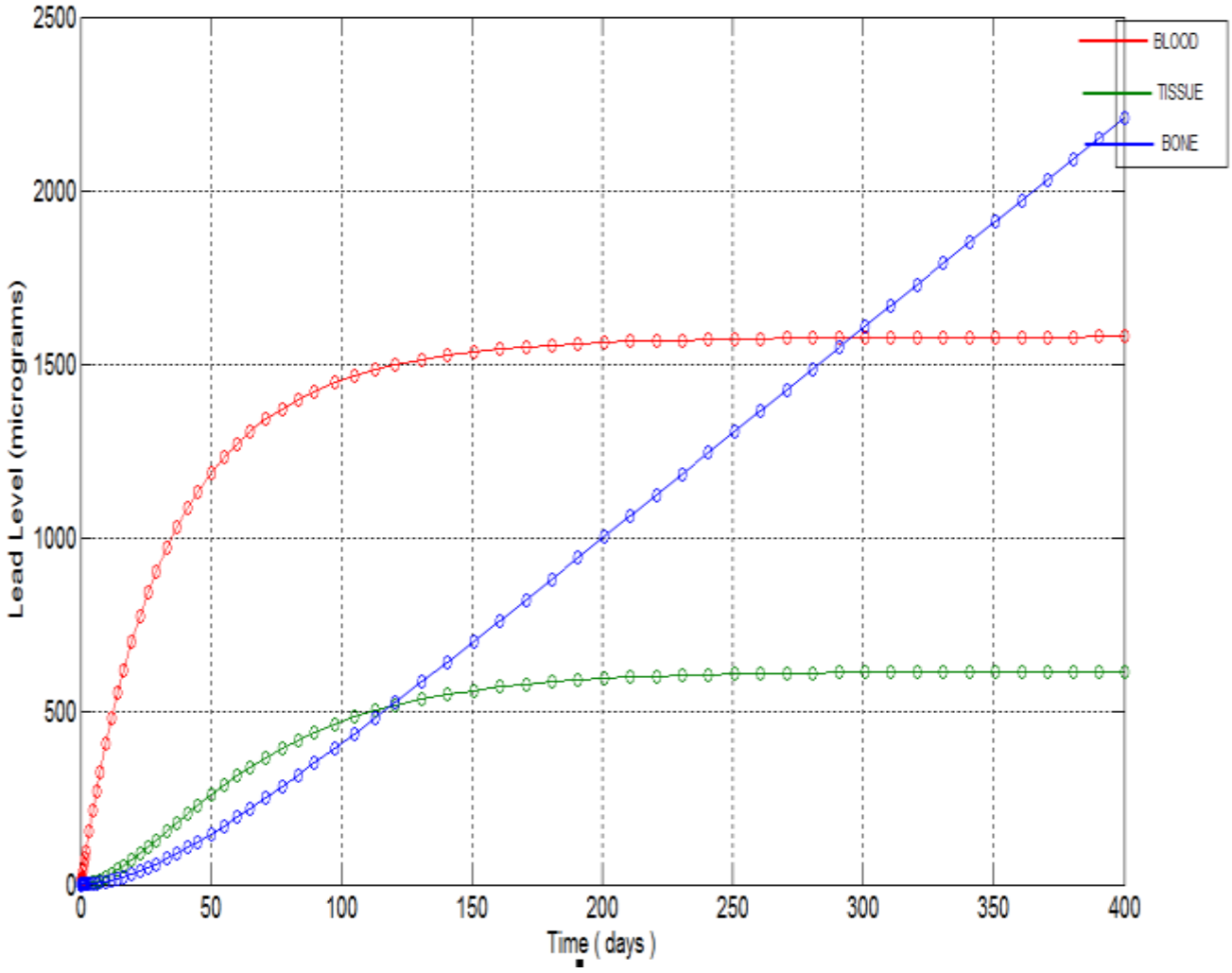



Fig. 4.2 After 400 days, plot of the model.

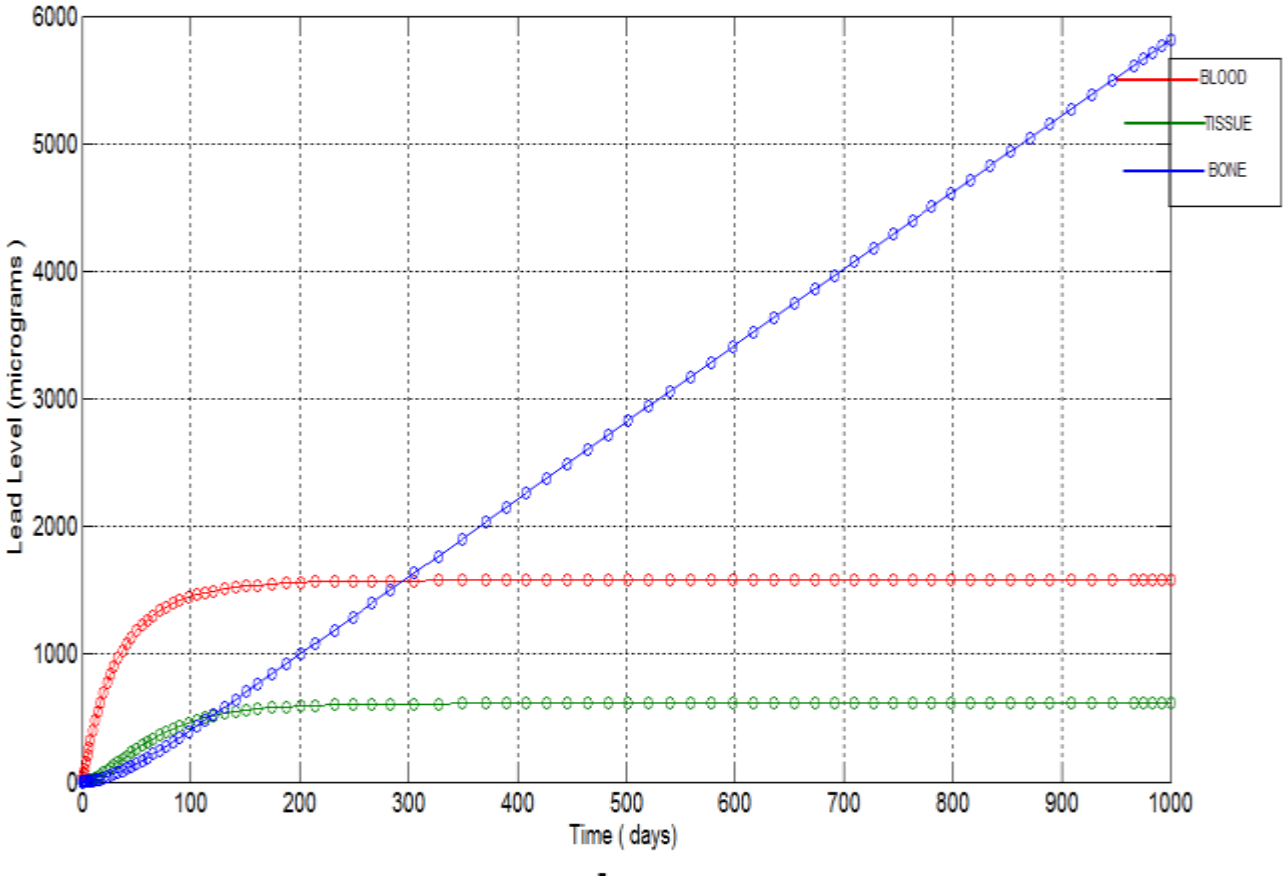



Fig.4.3 After 1000 days, plot of the model

## 4.5 Sensitivity Analysis

To improve the subject's health condition, some further assumptions are applied to the system.

### 4.5.1 Non-lead Environment

Suppose 400 days later, the person moves to non-lead environment. The value N in the equation is the total quantity of lead intake per day because from previous equations only N is related to the intake quantity directly from the outside environment. For this case, the value N is arranged be a step function, $49.3(400 - t)$ by (Batschelet et al. 1979). After 400 days, the lead is gradually taken out of the body because the intake rate goes to zero. The graph (Fig 4.4) shows quick drop of the lead level after 400 days, then reaches to zero in the blood and the tissues. Even the level in the bones changes behavior to horizontal movement, although it does not drop to zero.

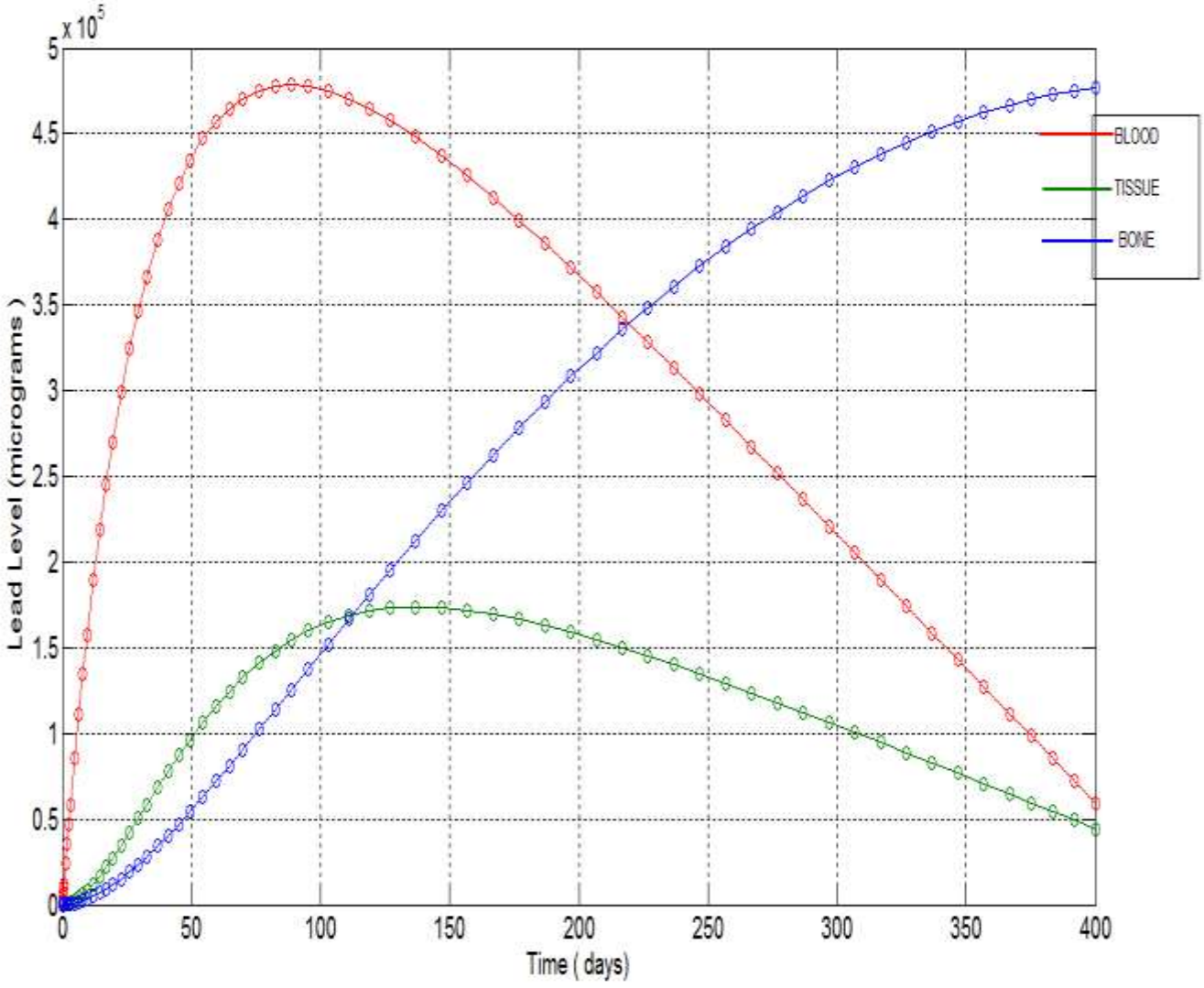



Fig. 4.4 plot of the model for non-Lead environment

### 4.5.2 Small Lead Environment

The non-lead environment is not realistic for this industry, so if the lead level is reduced (the subject moves to a rural area or quits smoking after 400 days), what behavior will the differential equations show? For this case, the value N is changed. The lead level of the body is reduced, but some quantity of lead is ingested by the step function. As a reasonable value, the intake rate is reduced from 49.3 to 33 by ( Borrelli). N is defined as N = 49.3 step(400−t)+33 step(t −400).The graph (Fig4.5) shows the drop of the lead in the blood and the tissues, but the level in the bones

still increases. This tells us that it is difficult to take the lead out of the bones by decreasing the lead intake.

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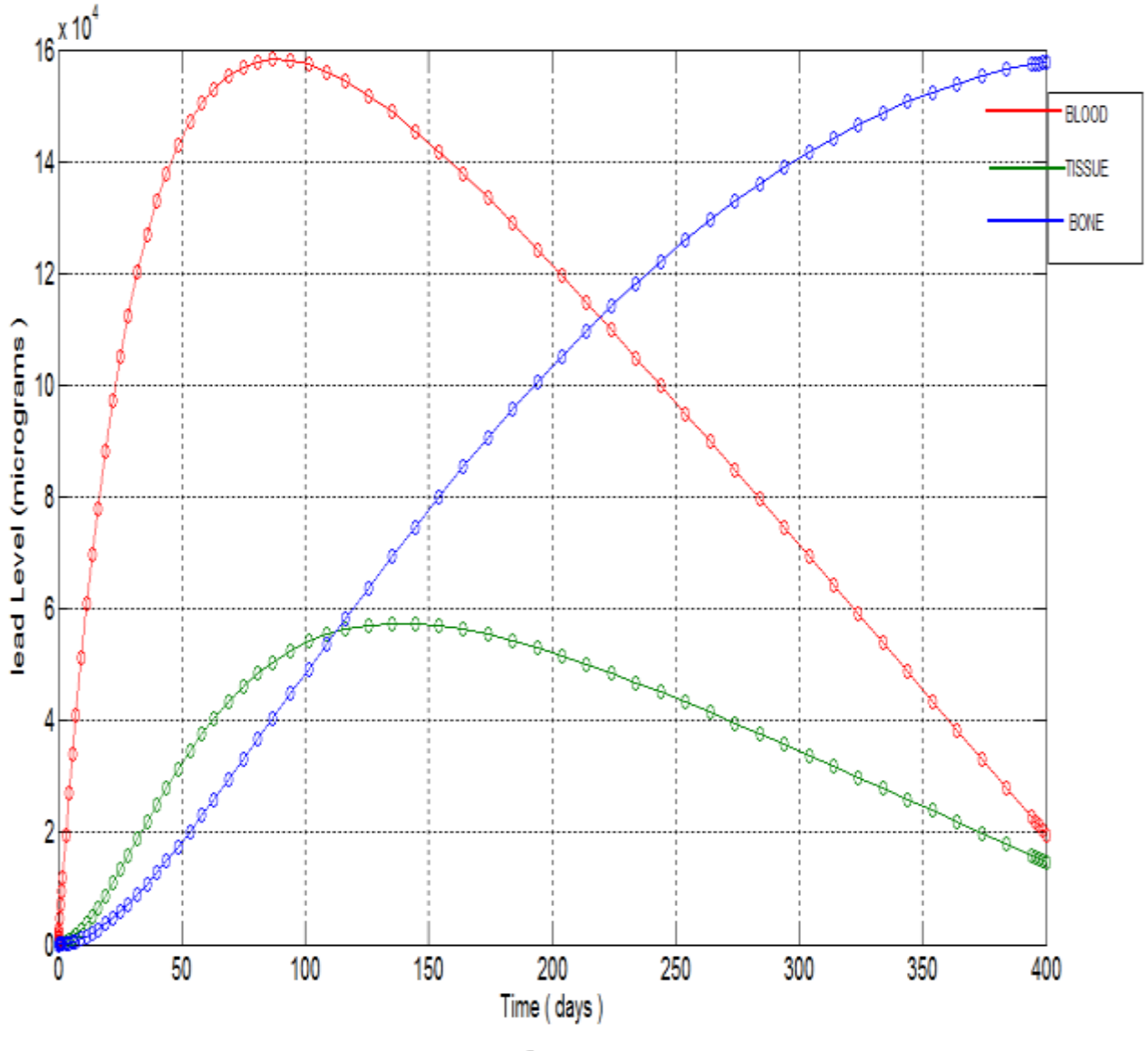


Fig.4.5 Plot of the model for a small lead environment

### 4.5.3 Medication

Suppose that the subject stays in the same area, but he decides to take medication to reduce the lead level in his body. The medication works to increase the rate of excretion of lead through the urine by a factor of 10. This affects the coefficient of $e_1$, and indirectly the coefficient value of $A_{11}$ in the system. The first equation now becomes

$$Y'_1 = (-0.3611)Y_1 + \frac{1088}{87500}Y_2 + \frac{7}{200000}Y_3 + 49.3$$

Plotting the system we now have,

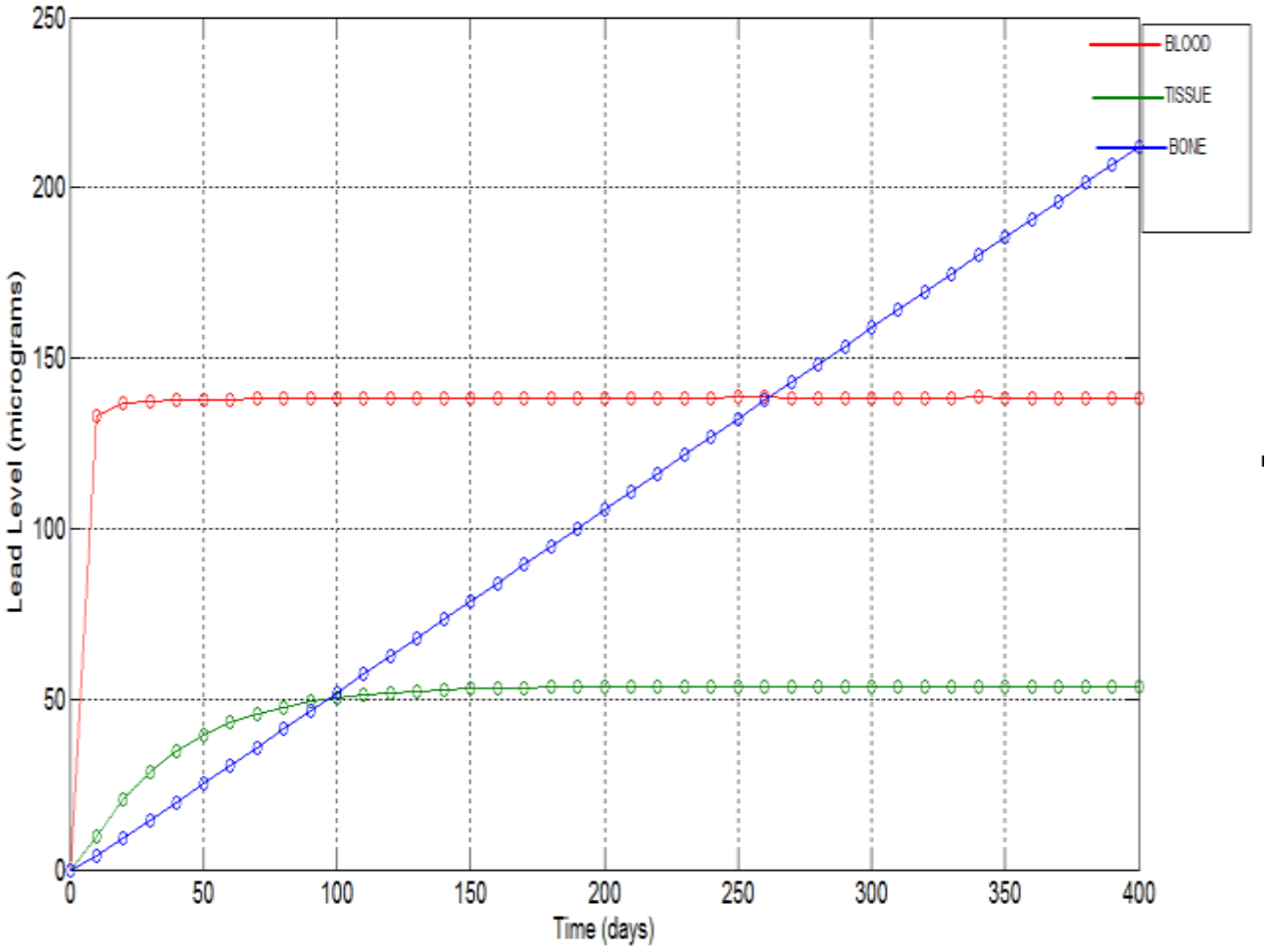

Fig4.6 Plot of the model with medication

### 4.5.4 Non-Lead Environment Plus Medication

Suppose 400 days later, the person moves to non-lead environment with medications. The value N in the equation is the total quantity of lead intake per day because from previous equations only N is related to the intake quantity directly from the outside environment. For this case, the value N is arranged be a step function, 49.3(400 − t). The first equation now becomes

$$Y'_1 = (-0.3611)Y_1 + \frac{1088}{87500}Y_2 + \frac{7}{200000}Y_3 + 49.3(400 - t)$$

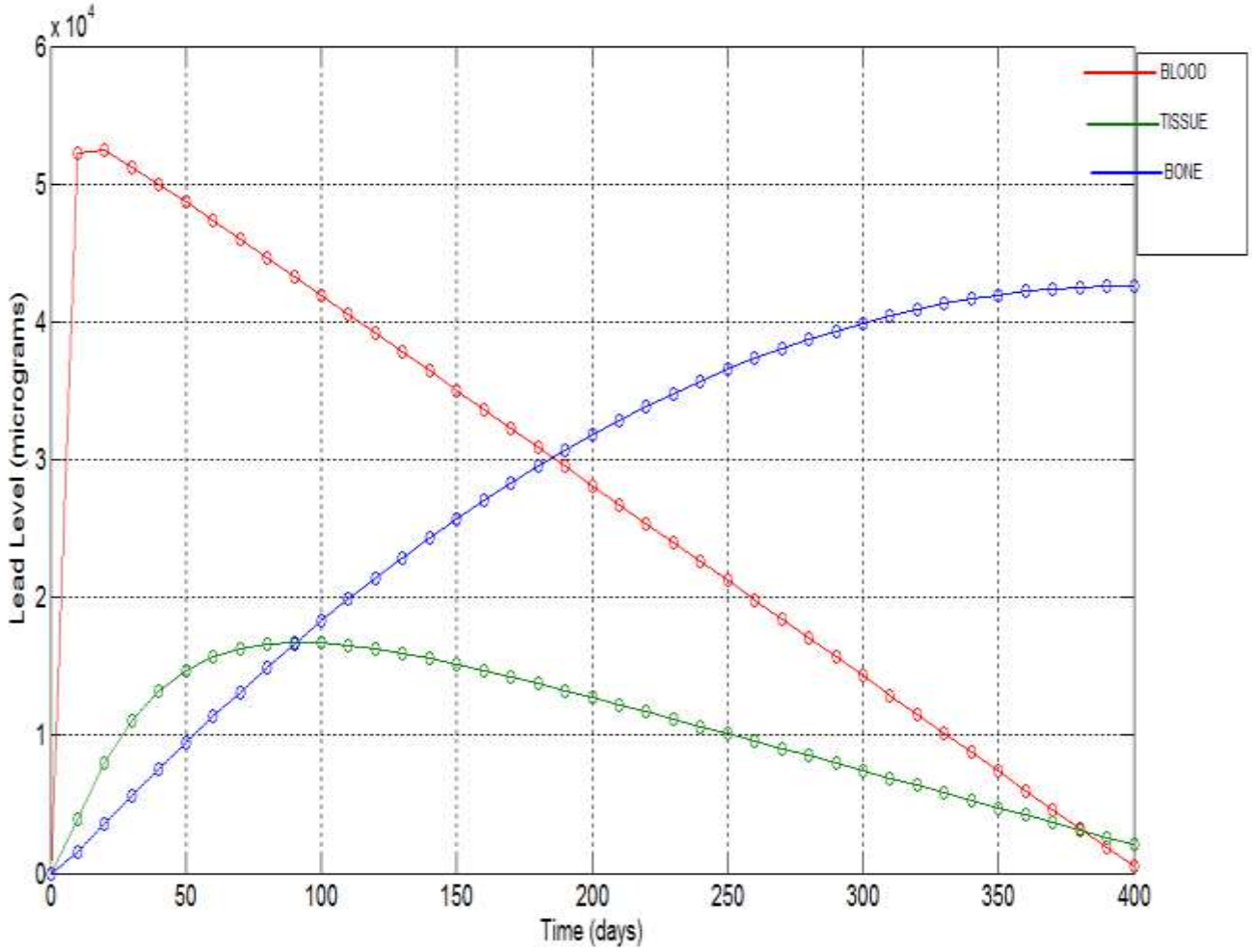


Fig4.7 Plot of the model for non-Lead environment with medication

### 5.5.5 Small Lead Environment Plus Medication

The non-lead environment is not realistic for this industry, so if the lead level is reduced (the subject moves to a rural area or quits smoking after 400 days). The lead level of the body is reduced, but some quantity of lead is ingested by the step function. As a reasonable value, the intake rate is reduced from 49.3 to 33 by ( Borrelli). N is defined as N = 49.3 step(400−t)+33 step(t −400). The first equation becomes**,**

$$Y'_1 = (-0.3611)Y_1 + \frac{1088}{87500}Y_2 + \frac{7}{200000}Y_3 + 49.3(400 - t) + 33(t - 400)$$

From the graphs (Fig4.8 and Fig4.9) below, we can see that the amount of lead in the blood and the tissue get to zero. Even the level in the bones changes behavior to horizontal movement, although it does not drop to zero.

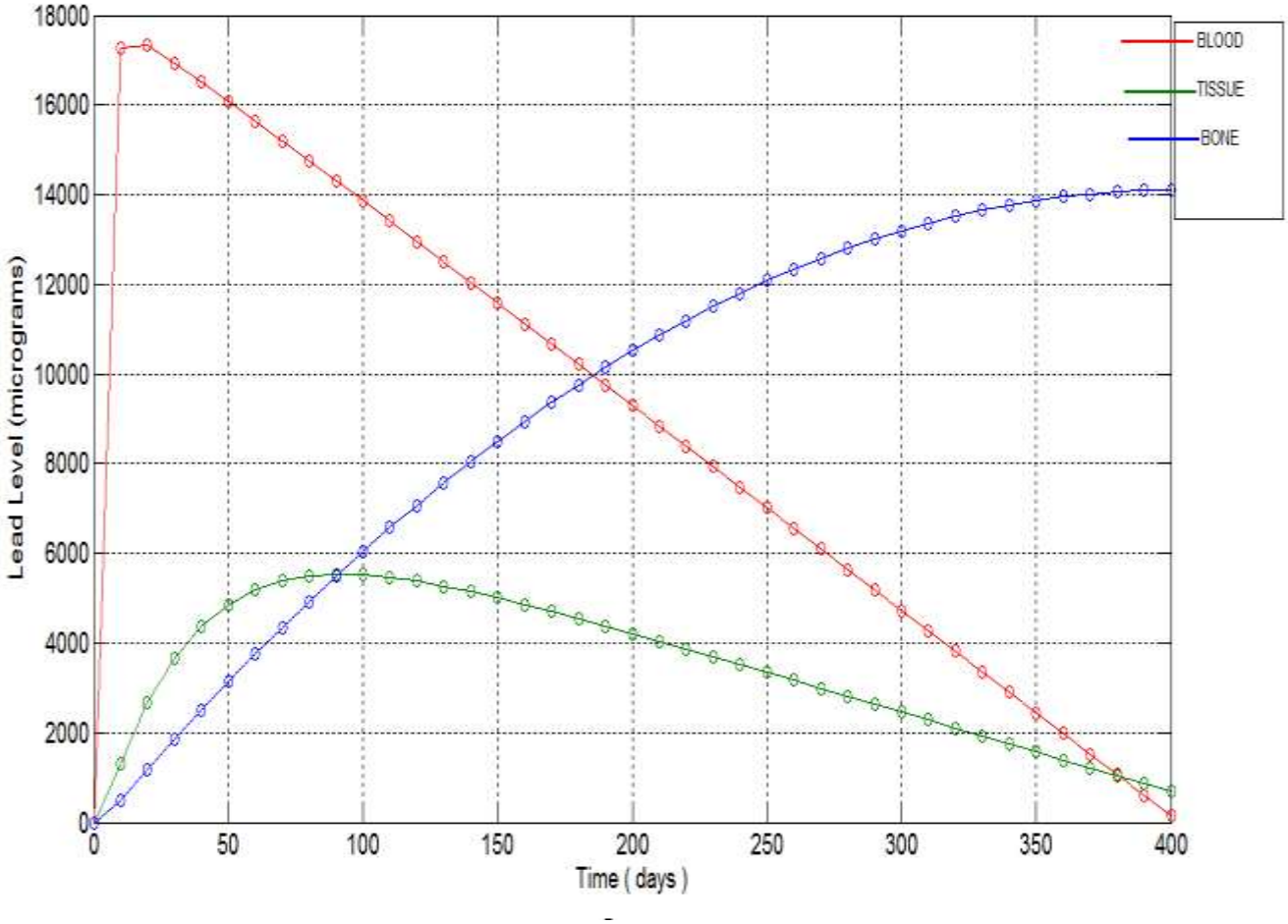


Fig4.8 Plot of the model for small-Lead environment with medication

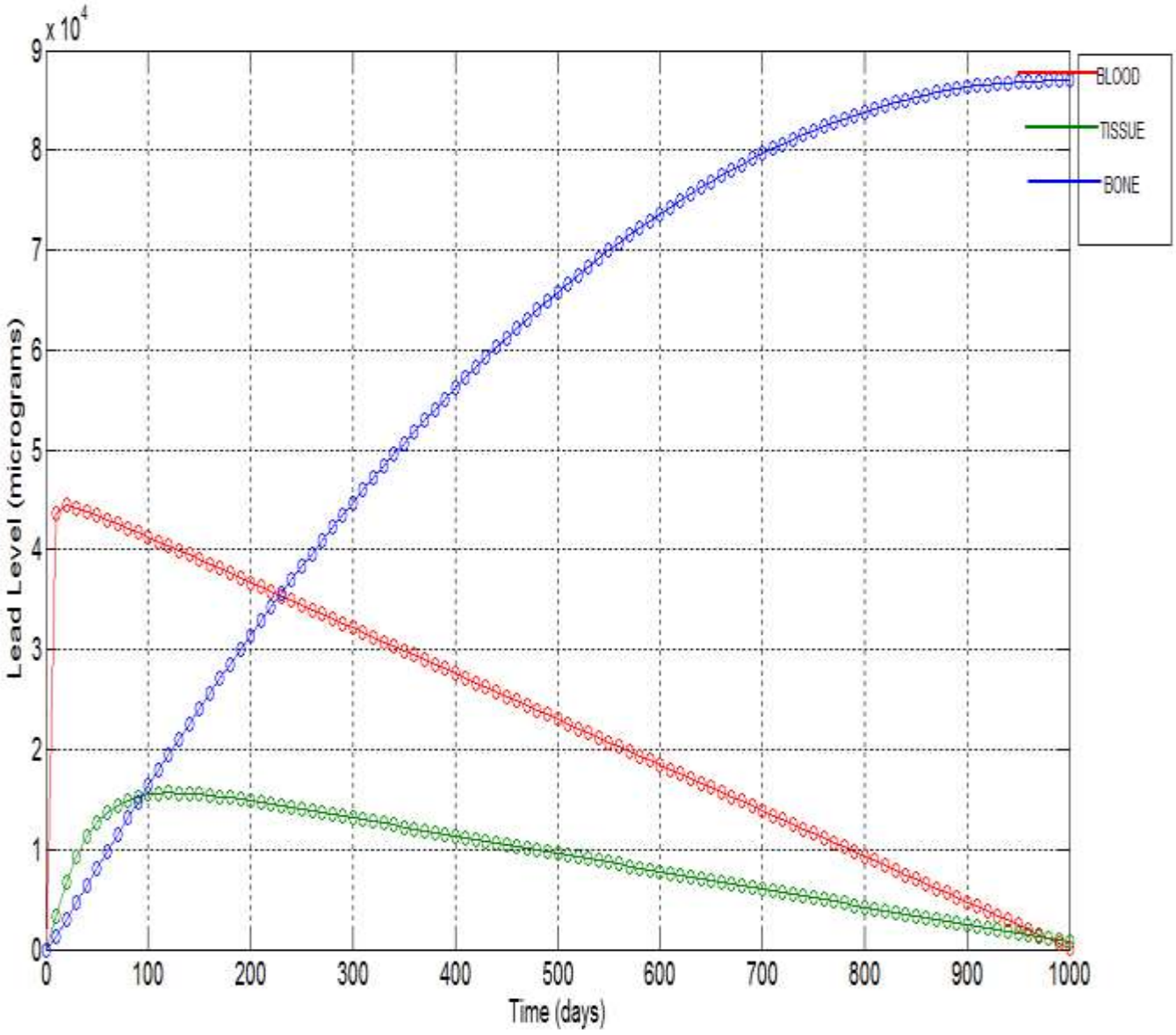


Fig 4.9 Plot of the model for small-Lead environment with medication( 1000days)

# CHAPTER FIVE

# CONCLUSION AND RECOMMENDATION

## 5.1 Conclusion

At the end of our analysis, the solution is given by

$$X(t) = X_c(t) + X_p(t)$$

Where $X_c(t)$ the transient is state solution and $X_p(t)$ is the steady state solution. Hence $X_c(t)$ is the transient solution that depends only on the initial conditions and $X_c(t) \rightarrow 0$ as $t \rightarrow \infty$

As $X_c(t) \rightarrow 0$, the solution $X(t)$ is given as $X(t) = X_p(t)$ where $X_p(t)$ is obtained from the external deriving forces.

Finally, we observed that moving the subject from the lead environment to a non-lead or a small lead environment with medication reduces the lead content in the system drastically.

Therefore, from the graphical analysis, it is reasonable to apply those assumptions to real life situations

## 5.2 Recommendation

We recommend that further studies could be done to determine the kinetics of other metallic elements like Zinc in the human body.

Finally, we could not get the data from Ghana and was obtained from Southern California because of time and financial constraints; we therefore recommend that for any further studies, the data should be obtained from the research location

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