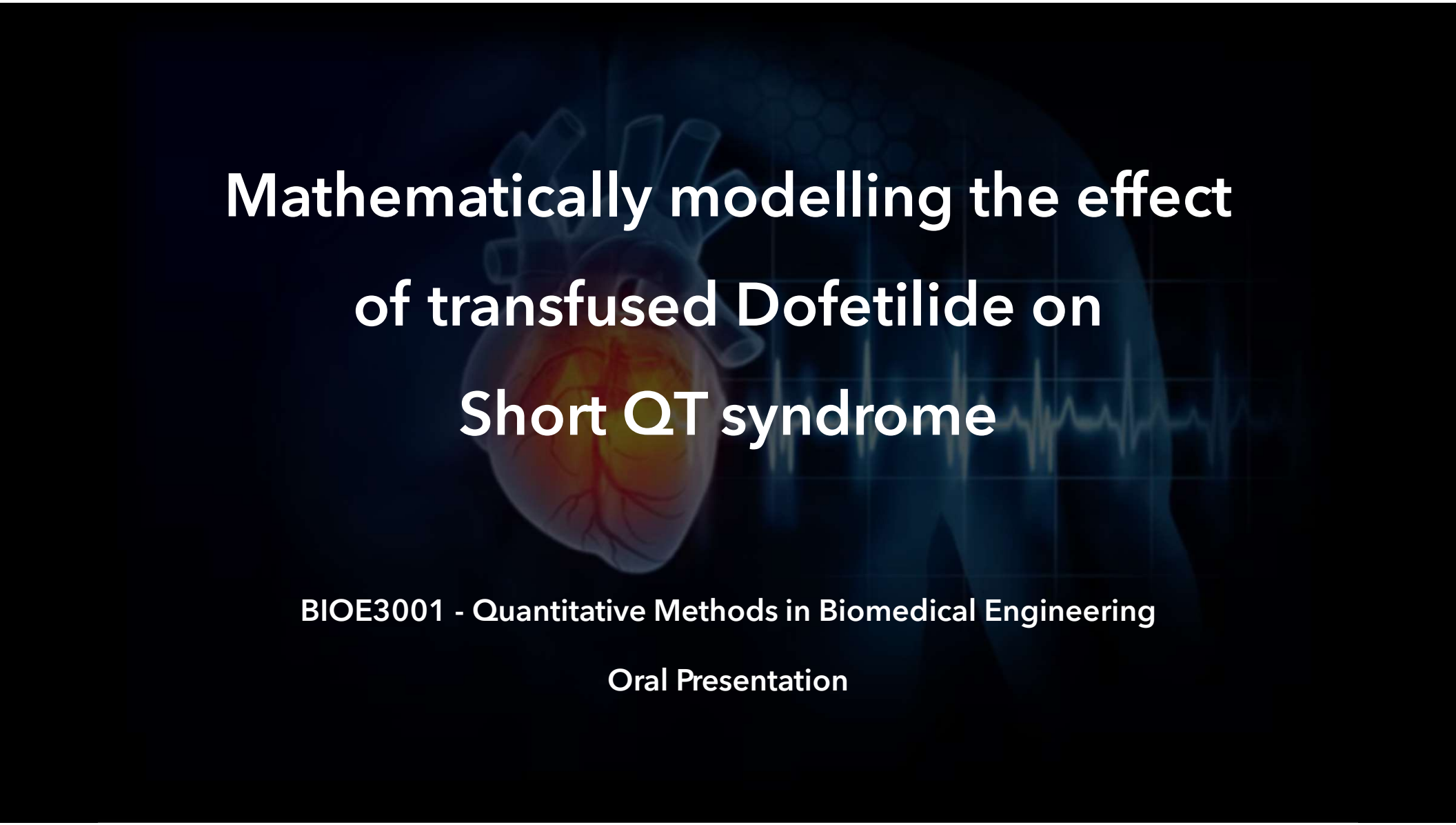


Mathematically modelling the effect of transfused Dofetilide on Short QT syndrome

BIOE3001 - Quantitative Methods in Biomedical Engineering

Oral Presentation

Clinical Background

Short QT syndrome (Type 1)

A cardiac disorder which generates short QT intervals [1]

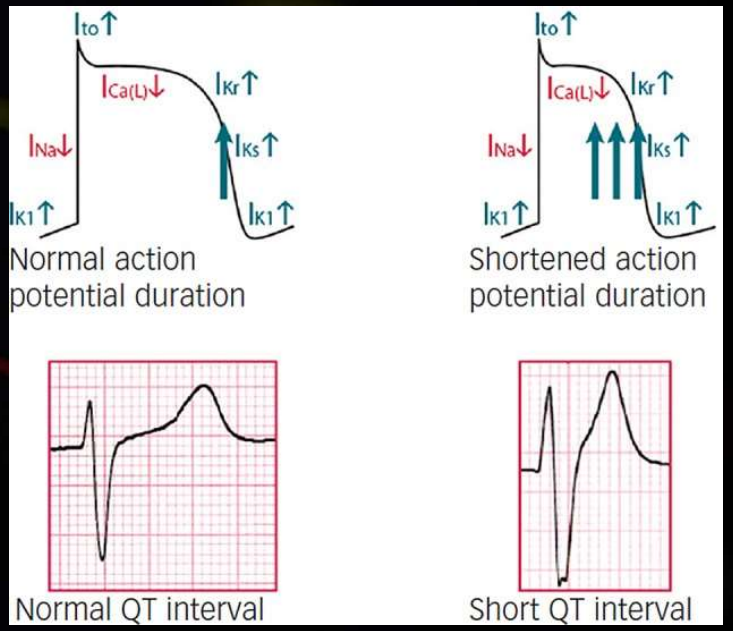


Figure 1: Mechanism of Short QT syndrome, from [11]

Root Cause:

Mutations in the KCNH2 (hERG) gene

- Responsible for regulating k+ channels that generate cardiac muscles [2]

Clinical Problem - Biostatistics

Symptoms [5]:

- Sudden Cardiac Arrest
- Heart Palpitations
- Sudden Fainting

Statistics:

Individuals with syndrome: ~ **1.6 million to 16 million** individuals

Globally predicted to have Short QT syndrome, from: [6]

Healthcare Cost: **$300 Billion USD / year**

Predicted global cost for those that experience sudden cardiac arrest, from [10]

Clinical Problem – Current Treatments

Dofetilide

"An Antiarrhythmic agent used to calibrate atrial fibrillation to the normal sinus rhythm" From: [7]

1. Binds to potassium channels in cardiac tissue
2. Inhibits potassium channels
3. Prolongs action of action potential
4. Increases duration of QT interval on EKG graph

Sources: [7], [8], [9]

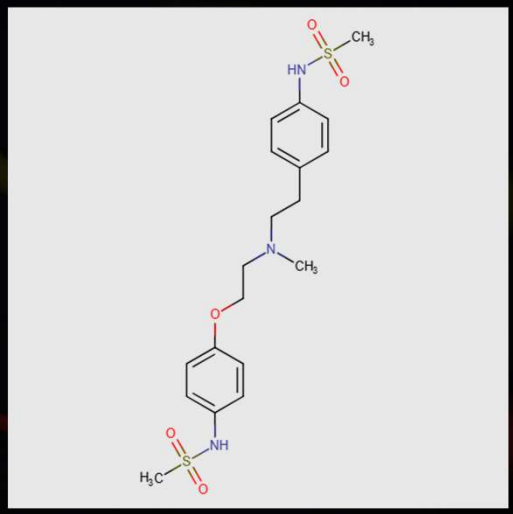


Figure 2: Molecular representation of Dofetilide, from [7]

We must create an effective model that is able to help clinicians to optimize Dofetilide therapy for patients diagnosed with Short QT Syndrome

Model Parameters

Table 1: Parameters for treatment model

Mathematical Symbol/Equation	Units	Name	Description
C_{Dof}	ng/mL	Dofetilide concentration	Concentration of Dofetilide plasma within subject patient's blood
$Interval_{QT}$	Ms	QT Interval	Time duration of EKG QT interval
$Interval_{OG}$	Ms	QT Interval OG	Time duration of original QT interval for untreated patient
D_{Dof}	ng	Dofetilide dosage	Dosage amount for diagnosed patient (clinically administered)
$t_{effective}$	hours	Effective drug time	Time required for Dofetilide to have detectable therapeutic effect
t_{max}	hours	Maximum drug time	Maximum time Dofetilide has therapeutic effect on potassium channel
k_{decay}	hours	Dofetilide decay	Half life decay of Dofetilide in the body
V_{Dist}	L/kg	Volume Distribution	Dofetilide plasma volume relative to subject patient's blood volume
B_{Dof}	-	Protein Binding %	Percentage of drug concentration that binds to proteins in cardiac tissue
O_{Dof}	-	Oral absorption %	Percentage of drug that gets absorbed from intestinal system

Estimated and Researched Values

Table 2: Researched Values from literature

Mathematical Symbol	Units	Value	Resource (if applicable)
k_{decay}	hours	10	[7], [8]
V_{Dist}	L/kg	3L/kg	[7], [8]
B_{Dof}	-	70%	[7], [8]
O_{Dof}	-	90%	[7], [8]

Assumptions

1. Body weight of patient: 70kg
2. No external factors or events affect patient heart rate during study observation

Simplifications

1. Method of drug secretion from urine and feces grouped together to have 100% secretion rate as part of k_{decay} [8]

Mass Volume

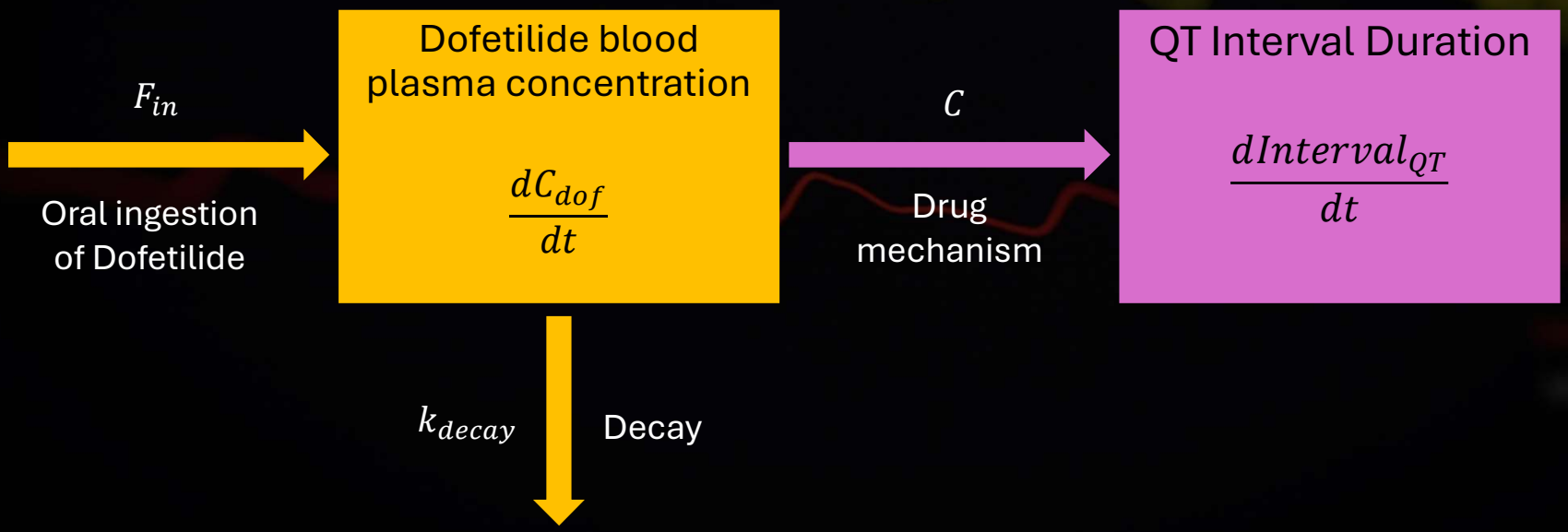


Figure [3]: Model for Short QT Syndrome treatment with Dofetilide

Diagrams

Blood concentration

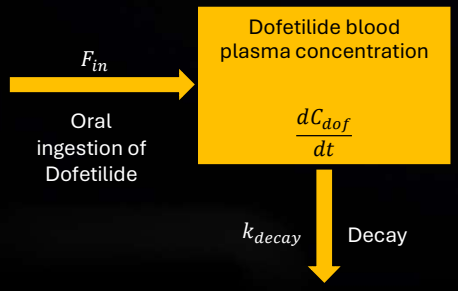
Change of blood Dofetilide concentration in patient blood over time

Utilises Dataset 3

$$\frac{dC_{dof}}{dt} = \begin{cases} F_{in}, & t < t_{effective} \\ F_{in} - k_d D_{dof}, & t_{effective} \leq t < t_{max} \\ -k_d D_{dof}, & t \geq t_{max} \end{cases}$$

Where:

$F_{in} = \frac{D_{Dof} * O_{Dof}}{V_{Dist}}$, from [8], [9]



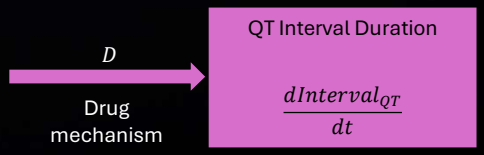
QT Interval

Change of average QT EKG interval over time

Utilises Dataset 2

Since $\frac{dInterva_{QT}}{dt} \propto \frac{dC_{dof}}{dt}$,

$$\frac{dInterval_{QT}}{dt} = \begin{cases} k_d * D_{dof} + dInterval_{OG} & t_{effective} \leq t < t_{max} \\ dInterval_{OG} - (UNSURE), & t \geq t_{max} \end{cases}$$



Predicted system outcomes

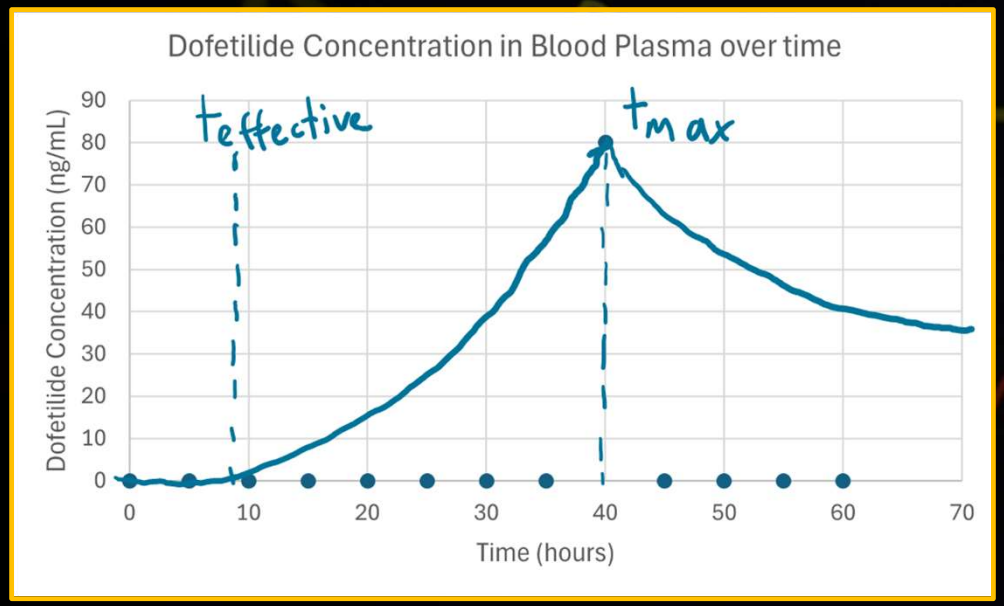


Figure 4: Predicted Dofetilide concentration in blood over time

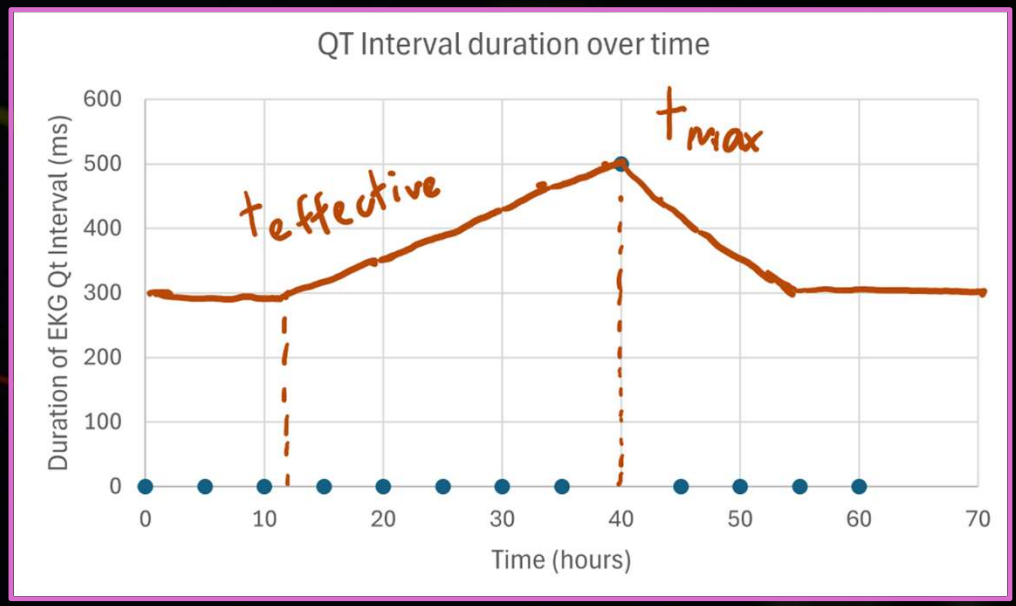


Figure 5: Predicted change of QT Interval duration over time

Further development

1. Use ECG data to work out untreated QT interval time and use that to select clinical dosage, according to [9]
2. Work on pharmacodynamics to find relation between drug effect on QT interval (MM)?

Thank You

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