Problem Set 2

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Clint Valentine
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Biomolecular Control and Dynamics
Prof. Anand Asthagiri

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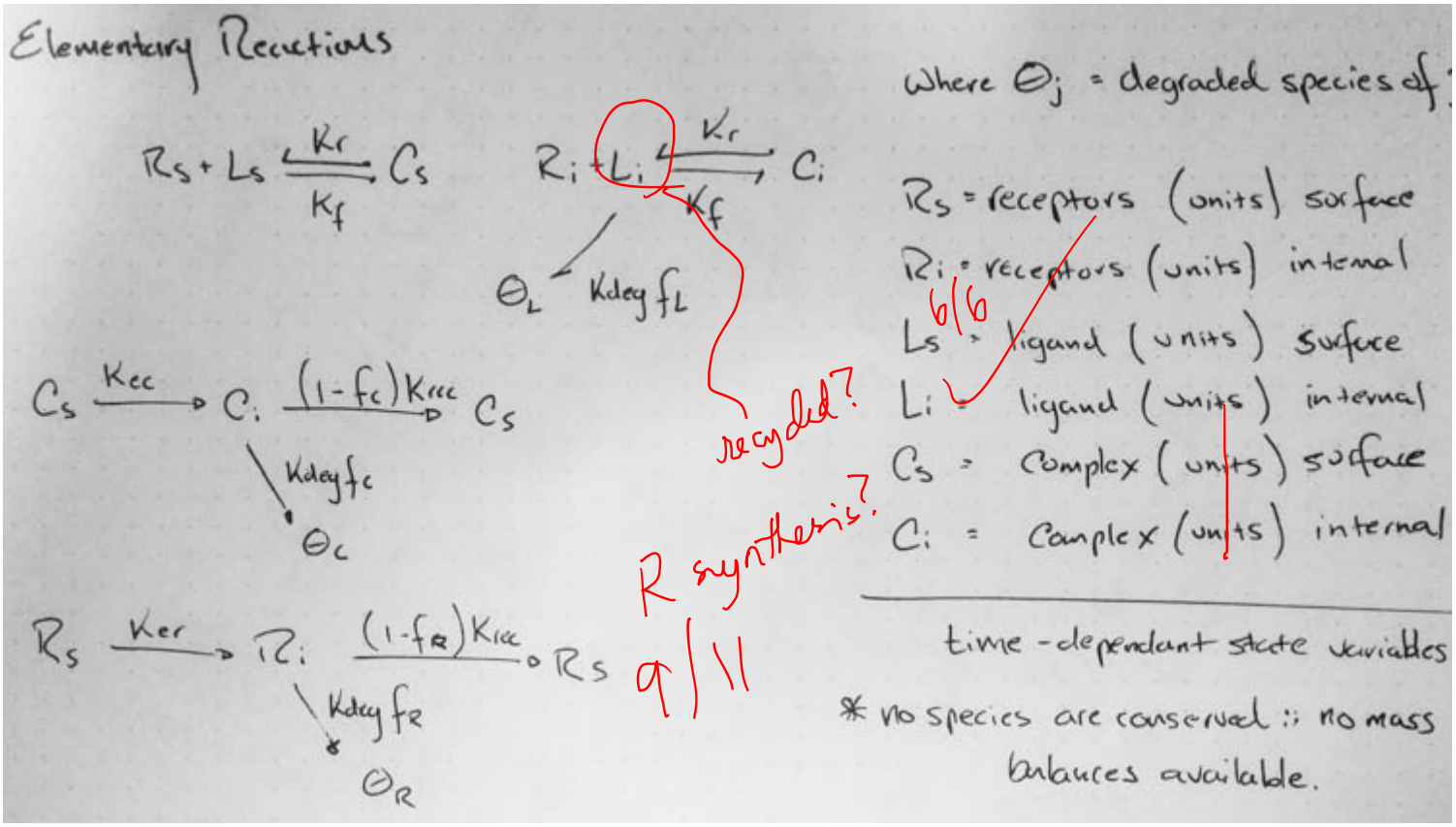
Modeling Receptor-Ligand Trafficking

To model the receptor-ligand trafficking system as proposed in the Problem Set #2 prompt we first make the assumptions that free surface ligand cannot enter an endocytic vessel unless bound to a surface receptor. We also assume that all outputs of the system, θ_j where j is equal to degraded species, disappear from the system and have no feedback. We also assume that because all species are degraded at some defined rate that there are no conserved species and therefore no mass balances in this system. 2/2



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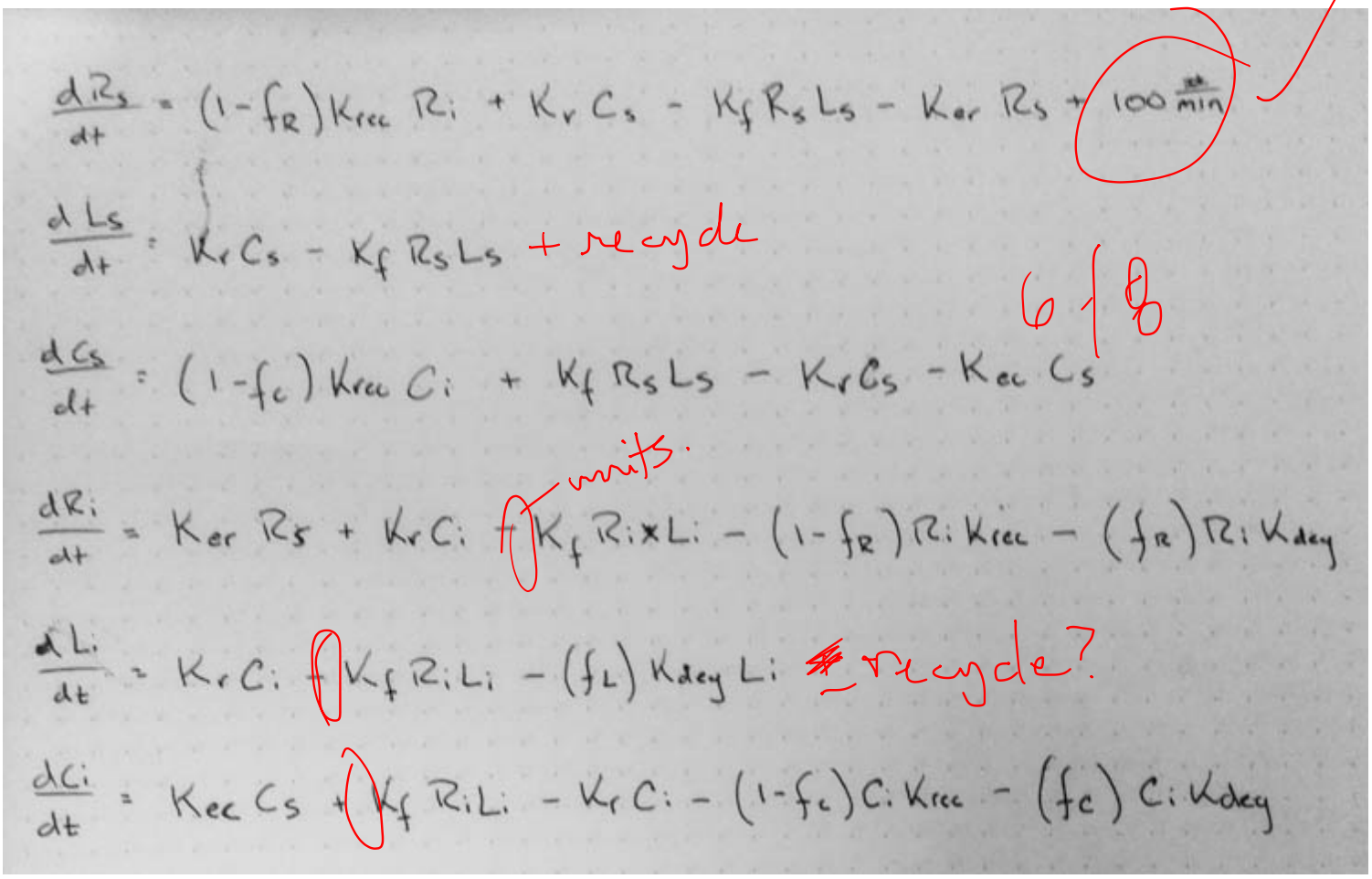
The rate laws defined are the rates of all of the variables in the system which are all time-dependent state variables. We chose not to model θ_j because it would provide no useful information at the moment. The code below converts the concentration of ligand to the molecular units of ligand and




```
kf     = 0.07;  % 1/(M x min)
kr     = 0.3;   % 1/min
kec    = 0.3;   % 1/min
ker    = 0.03;  % 1/min
krec   = 0.06;  % 1/min
kdeg   = 0.002; % 1/min
fdegr  = 0.2;
fdegl  = 0.2;
fdegc  = 0.5;
rsynth = 100;   % units/min

% This function solves the system for no ligand (internal or external)

syms Rs(t) Ri(t);
b = dsolve(...
    diff(Ri, t) ==  ker*Rs -(1-fdegr)*krec*Ri -fdegr*kdeg*Ri,...
    diff(Rs, t) == -ker*Rs +(1-fdegr)*krec*Ri +rsynth,...
    Rs(0) == 0, Ri(0) == 0);

sRi = eval(limit(b.Ri, inf)); % steady-state at t=inf
sRs = eval(limit(b.Rs, inf)); % steady-state at t=inf

fprintf('Stable-state Ri per cell = %g\n', sRi);
fprintf('Stable-state Rs per cell = %g\n', sRs);
```

```
% Assuming ligand is added when receptor expression maintains a
% steady-state level.

cells = 5e5;   % Units
Lo = 1e-9;     % Molar
Volume = 3e-3; % Liters
Av = 6.02214129e23; % Avagadro's Number

iRi = cells * sRi;
iRs = cells * sRs;
iCi = 0;
iCs = 0;
iLi = 0;
iLs = Lo * Volume * Av;

% Function code in ps2function.m kept in same directory
% function f = ps2function(t,Y)
%     f(1,1)= -.048*Y(1)+.03*Y(2)-7.2*10^-7*Y(1)*Y(5)+.3*Y(3)-.0004*Y(1);
%     f(2,1)= .048*Y(1)-.03*Y(2)-7.2*10^-7*Y(2)*Y(6)+.3*Y(4)+100;
%     f(3,1)=-.03*Y(3)+.3*Y(4)+7.2*10^-7*Y(1)*Y(5)-.3*Y(3)-.001*Y(3);
%     f(4,1)=.03*Y(3)-.3*Y(4)+7.2*10^-7*Y(2)*Y(6)-.3*Y(4);
%     f(5,1)=-7.2*10^-7*Y(5)*Y(1)+.3*Y(3)-.0004*Y(5);
%     f(6,1)=-7.2*10^-7*Y(6)*Y(2)+.3*Y(4);
% end

sol = ode45(@ps2function,[0 4], [iRi iRs iCi iCs iLi iLs]);

time = sol.x;
Lsplot = sol.y(6,:);
Lpoundplot = sol.y(3,:) + sol.y(5,:);
Csplot = sol.y(4,:);

plot(time, Lsplot, time, Lpoundplot, time, Csplot);

h = xlabel('Time (min.)', 'FontSize', 12);
set(h, 'Interpreter', 'latex');
h = ylabel('Molecular Units $\cdot$ $10^{10}$', 'FontSize', 12);
set(h, 'Interpreter', 'latex');
h = title('Time Evolution of Surface Complex and Ligands', 'FontSize', 12);
set(h, 'Interpreter', 'latex');

grid on;
legend('Ls', 'L#', 'Cs');
```

```
Stable-state Ri per cell = 250000
Stable-state Rs per cell = 403333
```

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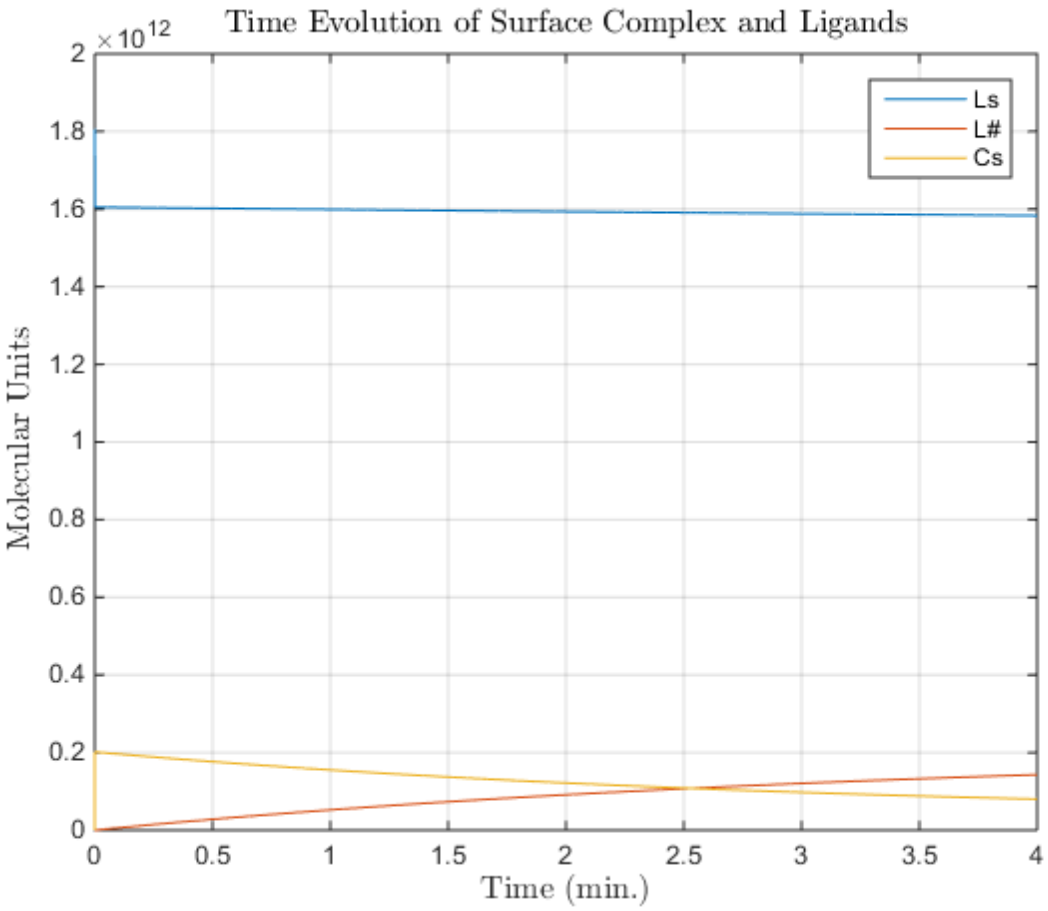

The plot shows that total surface ligand is immediately consumed in a 1:1 ratio for the available steady-state receptors on the surface of the cells in solution. This happens on a time scale which appears instantaneous. Over time surface ligand is consumed through the system and degraded. This occurs slowly as receptor synthesis attempts to keep up with the high intial ligand concentration. The quantity of internal ligand increases with time starting at a value of zero. We hypothesize that this value will reach zero ligand as time goes to infinity. We expect this because no new stock of ligand are supplied and ligand is continually degraded at a set rate.

We simulated this for four minutes which took an excess of 15 computaional minutes. With more computation time, it would be interesting to see if our hypothesis is supported.

Enzyme Kinetics

1. Product formation is the greates at initial time (i.e. $t = 0$) because of the equation derived from complex formation at quasi-steady state: $\frac{dP}{dt} = \frac{k_2 E_o S}{K_m + S}$ When $\frac{dP}{dt}$ is at $t = 0$ substrate concentration is at its highest. As time passes, substrate concentration decreases which corresponds to lesser values of $\frac{dP}{dt}$ until substrate is nearly exhausted $S = 0$. As $\lim_{t \to \infty}$ the value for $\frac{dP}{dt}$ nears zero due to subtrate nearing 0 mM.

1. By examining the Michaelis-Menten graph of reaction velocity vs. substrate concentration it is apparant that the maximum velcocity is when substrate concentration increases to infinity. The value for V_{max} is theoretical because of this non-realistic infinity parameter. As substrate concentration increases more of the enzymes will be in the bound state and actively catalyzing product formation. Only when there is such a high concentrate of substrate that an enzyme has no idle time will the reaction reach the theoretical V_{max}

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