Models and Languages for Computational Systems Biology

Lecture 12: Larger Systems and Stochastic Kinetics

Ian Stark

School of Informatics
The University of Edinburgh

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Semester 2 Week 8

Previous Homework

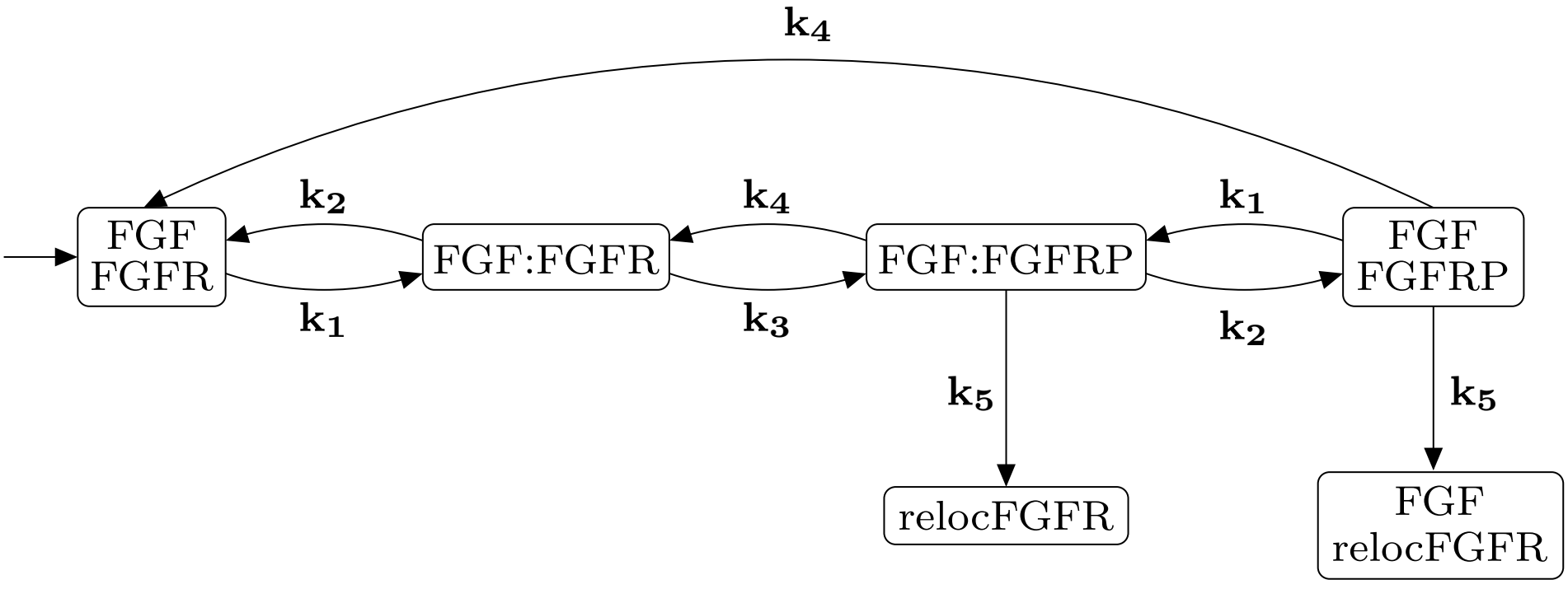
Read the remainder, §§4–6, of the tutorial article.

Marta Kwiatkowska, Gethin Norman, and David Parker.
Probabilistic model checking for systems biology.
In *Symbolic Systems Biology: Theory and Methods*. Jones and Bartlett, 2010. To appear.

Lucas Laursen.
Computational biology: Biological logic.
Nature 462:408–410, 2009.

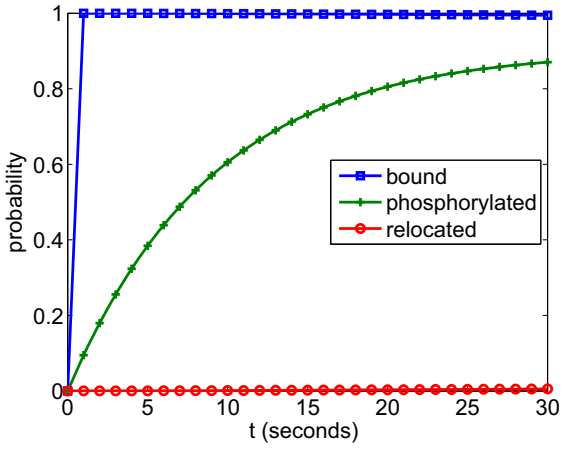
> In the meantime, however, Fisher and her fellow executable-biology enthusiasts have a lot of convincing to do, says Stephen Oliver, a biologist at the University of Cambridge, UK. "Modelling in general is regarded sceptically by many biologists," he points out.

Do you think this is true? Can you find any evidence for or against?

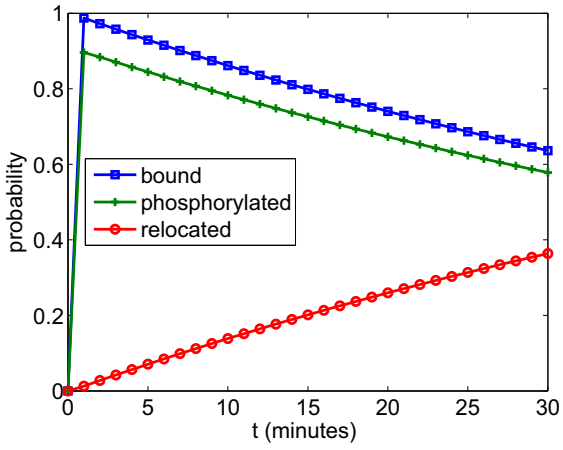

k4
k2
k4
k1
FGF
FGFR
FGF:FGFR
FGF:FGFRP
FGF
FGFRP
k1
k3
k2
k5
k5
relocFGFR
FGF
relocFGFR

```
const double k5 = 1/(60 * 60); // rate of relocation

module FGF

    fgf : [0..2] init 0; // 0 - free, 1 - bound, 2 - removed from system

    [bind] fgf=0 → (fgf'=1); // FGF and FGFR bind
    [rel] fgf=1 → (fgf'=0); // FGF and FGFR unbind
    [reloc] fgf=1 → (fgf'=2); // FGF disappears since bound when FGFR relocates

endmodule
```

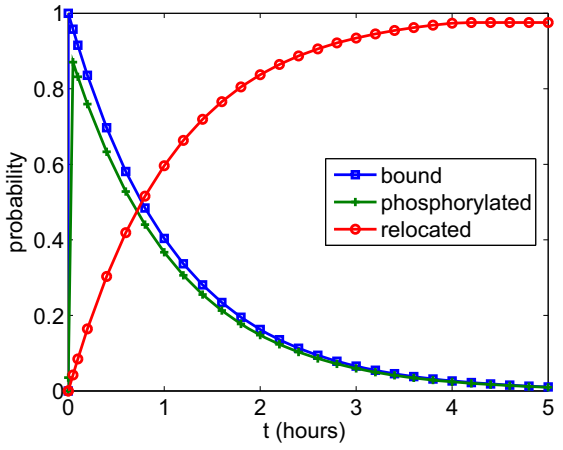
- $(phos{=}1) \Rightarrow \mathtt{P}_{>0.1}[\ \mathtt{true}\ \mathtt{U}^{[0,t]}\ (reloc{=}1)\ ]$ - 'if FGFR is currently phosphorylated, then the probability of it being relocated within the next t seconds is greater than 0.1';
- $(phos{=}1 \wedge fgfr{=}0) \Rightarrow \mathtt{P}_{\leq 0.2}[\ (fgfr{=}0)\ \mathtt{U}\ (reloc{=}1)\ ]$ - 'if FGFR is phosphorylated and free, then the probability of it being relocated before binding to FGF is at most 0.2';
- $\mathtt{P}_{=?}[\ \mathtt{true}\ \mathtt{U}^{[t,t]}\ (fgf{=}1)\ ]$ - 'the probability that FGF is bound to FGFR at time instant t (i.e. after exactly t seconds)';
- $\mathtt{P}_{=?}[\ \mathtt{true}\ \mathtt{U}\ (reloc{=}1 \wedge fgf{=}2)\ ]$ - 'the probability that FGFR relocates and FGF is bound when relocation occurs';
- $\mathtt{S}_{=?}[\ (fgf{=}0)\ ]$ - 'the probability that, in the long run, FGF is free';



(a) Time scale seconds



(b) Time scale minutes



(c) Time scale hours

Fig. 7. Transient properties of FGFR for the model of Figure 4

Populations Larger Than One

That was for the interaction of an individual molecule of FGF (*fibroblast growth factor*) and its receptor. The next step is to model systems of several individuals.

All extracts from:

Marta Kwiatkowska, Gethin Norman, and David Parker.
Probabilistic model checking for systems biology.
In *Symbolic Systems Biology: Theory and Methods*. Jones and Bartlett, 2010. To appear.

```
module POPULATION_MODEL

    fgf  : [0..N] init N; // free FGF
    fgfr  : [0..M] init M; // free FGFR (not phosphorylated)
    fgfrp  : [0..M] init 0; // free FGFR (phosphorylated)
    bnd  : [0..K] init 0; // bound FGF:FGFR (FGFR not phosphorylated)
    bndp  : [0..K] init 0; // bound FGF:FGFR (FGFR phosphorylated)
    reloc  : [0..M] init 0; // relocated FGFR

    // FGF and FGFR bind
    [] fgf>0 & fgfr>0 & bnd<K
        -> fgf * fgfr * k1   : (fgf'=fgf - 1) & (fgfr'=fgfr - 1) & (bnd'=bnd + 1);
    [] fgf>0 & fgfrp>0 & bndp<K
```

- $\texttt{P}_{=?}[\ \texttt{true U}\ (\mathit{reloc} \geq l_1 \wedge \mathit{fgf} \leq l_2)\ ]$ - 'the probability of reaching a situation where there are at least l_1 relocated FGFR receptors and the number of free FGF ligands is at most l_2';
- $(\mathit{bnd} > l_1) \Rightarrow \texttt{P}_{\geq 0.7}[\ \texttt{true U}^{[0,t]}\ (\mathit{reloc} \geq l_2)\ ]$ - 'if the number of FGF:FGFR compounds is greater than l_1, then the probability that the amount of relocated FGFR will reach l_2 within the next t seconds is at least 0.7';
- $\texttt{P}_{=?}[\ (\mathit{reloc}=0)\ \texttt{U}\ (\mathit{fgfp}=l)\ ]$ - 'the probability that l FGFR receptors are phosphorylated before any FGFR is relocated';

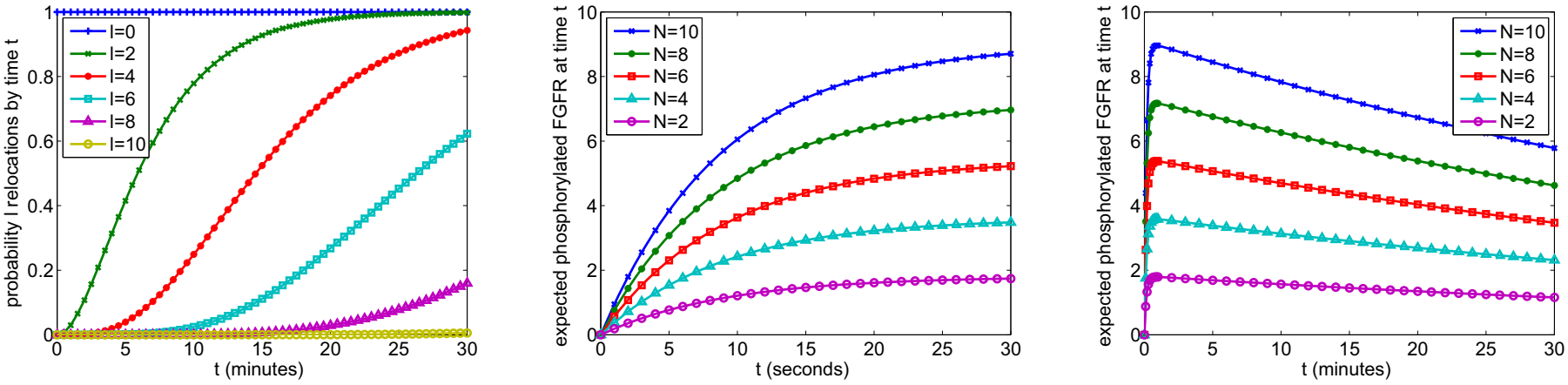


Fig. 11. Transient properties for the population example: (a) probability of l relocations by time t; (b/c) expected phosphorylated FGFR at time t (seconds/minutes).

Stochastic Kinetics

Daniel T. Gillespie.
Exact Stochastic Simulation of Coupled Chemical Reactions.
The Journal of Physical Chemistry 81(25):2340–2361, 1977

Daniel T. Gillespie.
Stochastic Simulation of Chemical Kinetics.
Annual Review of Physical Chemistry 2007.58:35–55.

We now follow slides from Gillespie's invited talk at CMSB 2007 in Edinburgh, which you can obtain online from the National e-Science Centre:

http://www.nesc.ac.uk/action/esi/contribution.cfm?Title=749

Alternate Reading

Wilkon's book presents the Gillespie algorithm in §§6.2–6.5. Chapter 8 then goes on to deal with approximation strategies for stochastic simulation.

D. J. Wilkinson.
Stochastic Modelling for Systems Biology.
Chapman & Hall/CRC, April 2006.

Yet More Advances in Algorithms

Improvements to Gillespie's algorithm, and the datastructures to support it, continue. Even a brief trip to Wikipedia reveals:

Alexander Slepoy, Aidan P. Thompson, Steven J. Plimpton
A Constant-Time Kinetic Monte Carlo Algorithm for Simulation of Large Biochemical Reaction Networks.
The Journal of Chemical Physics **128**, 205101 (2008).

Among other things, this points out connections to the general problem of *random variate generation* (RVG) for which both existing Gillespie-style algorithms and improvements are already well-studied, and further improvements are known. Allegedly.