

IO17 | Large Scale Bioinformatics for Immuno-Oncology

Introduction to different logic formalisms in CellNOpt

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A Toy model













System can reach steady state or oscillate

$\overline{x}_i(t+1) = \overline{B}_i(\overline{x}_{i1}(t), \overline{x}_{i2}(t), \dots, \overline{x}_{iN_i}(t)).$



Boolean simulation performed using pseudo-steady state





Algorithm penalizes lack of steady state, only effective for one 'early' time

Klamt, S., Saez-Rodriguez, J., Lindquist, J., Simeoni, L., Gilles, E. D., *BMC Bioinformatics*, 7:56,2006.

Training to data recovers structure

ligand

inhibitic

readout

EGF

EGFR

PI3K

TNFα

TNFR





Boolean 1-steady state recovers strong active links except feedback

EMBL-EBI



MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J Phys Biol 9 045003, 2012



Constrained Fuzzy Logic can handle quantitative differences



 Boolean modeling can **not** describe **quantitative** aspects (e.g. intermediate activation)



Constrained Fuzzy Logic



MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J Phys Biol 9 045003, 2012

How to model feedback effects?

ligand

inhibitio

readout

EGF

EGFR

PI3K

TNFα







Approximation of transient behaviour using multiple time-scales





- (i) Train $\tau = 1 \rightarrow$ get early events
- (ii) Train $\tau = 2 \rightarrow$ find gates not active at $\tau = 1$ that explain evolution from $\tau = 1$ to $\tau = 2$

Rough approximation of dynamics, still computationally efficient





Approximation of dynamics using synchronous simulation & multiple time-scales







EGF

EGFR

PI3K

ligand

inhibitio

SOS-1

TNFα

TNFR







From Boolean to continuous and dynamic models within CellNOpt





Based on ordinary differential equations derived from logic models using a continuous update function

$$\begin{array}{|c|} & A \\ \downarrow & \frac{dx_B}{dt} = \tau_B [f(x_A) - x_B] \\ \hline & B \end{array}$$









- Easily interpretable parameters
 - is the life-time of species i=0 node not functional >0 higher functionality

 $\begin{array}{l} {\rm strength \ of \ regulation \ j \rightarrow i} \\ {\rm =0 \ no \ edge} \\ {\rm >0 \ stronger \ interaction} \end{array}$

• Direct derivation from logic rules

Generalisation for OR gales			
x_1	x_2	$B(f(x_1), f(x_2)) = \dots$	
0	0	$0(1 - f(x_1))(1 - f(x_2)) +$	
0	1	$(1 - f(x_1))f(x_2) +$	
1	0	$f(x_1)(1 - f(x_2)) +$	
1	1	$f(x_1)f(x_2)$	

Concretion for OD motor





d/dt(tnfa) = 0*(1-tnfa_inh) %Note that this implies a continuous stimulus



d/dt(egfr) = ((tgfa^egfr_n_tgfa/(tgfa^egfr_n_tgfa+egfr_k_tgfa^egfr_n_tgfa)*(1+egfr_k_tgfa^egfr_n_tgfa)-egfr) * egfr_tauinv)*(1egfr_inh)

d/dt(casp8) = ((tnfa^casp8_n_tnfa/(tnfa^casp8_n_tnfa+casp8_k_tnfa^casp8_n_tnfa)*(1+casp8_k_tnfa^casp8_n_tnfa)-casp8) *
casp8_tauinv)*(1-casp8_inh)

d/dt(akt) = ((pi3k^akt_n_pi3k/(pi3k^akt_n_pi3k+akt_k_pi3k^akt_n_pi3k)*(1+akt_k_pi3k^akt_n_pi3k)-akt) * akt_tauinv)*(1akt_inh)



ligand inhibitic

readout

EGF

EGFR

PI3K

TNFα

TNFR







Different methods capture different aspects







From Boolean to continuous and dynamic models within CellNOpt





Broad spectrum of modelling formalism with different level of detail





Terfve C Cokelaer T MacNamara A Henriques D Gonçalves E Morris MK van Iersel M Lauffenburger DA Saez-Rodriguez J *BMC Syst Biol, 6:*133, 2012

22

Logic modeling to link protein signaling networks with functional signaling data

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