次元解析を用いた薬剤耐性モデリング

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Pathway Modeling

mass action (fundamental process)

$$A + B \to P \quad (k)$$
$$P \to A + B \quad (\ell)$$

$$\frac{d}{dt}[A] = -k[A][B] + \ell[P]$$
$$\frac{d}{dt}[B] = -k[A][B] + \ell[P]$$
$$\frac{d}{dt}[P] = k[A][B] - \ell[P]$$

$$\frac{d}{dt}([A] + [P]) = 0$$ A conservation

$$\frac{d}{dt}([B] + [P]) = 0$$ B conservation

→ Integrable! (logistic type)
(explicit expression of the solution)

$$\frac{d[P]}{dt} = k(\alpha - [P])(\beta - [P]) - \ell[P]$$

polymerization

$$A + A \to P \quad (k)$$
$$P \to A + A \quad (\ell)$$

$$\frac{d}{dt}[A] = -2k[A]^2 + 2\ell[P]$$
$$\frac{d}{dt}[P] = k[A]^2 - \ell[P]$$

1-attachement annihilates 2A
1-detachment creates 2A

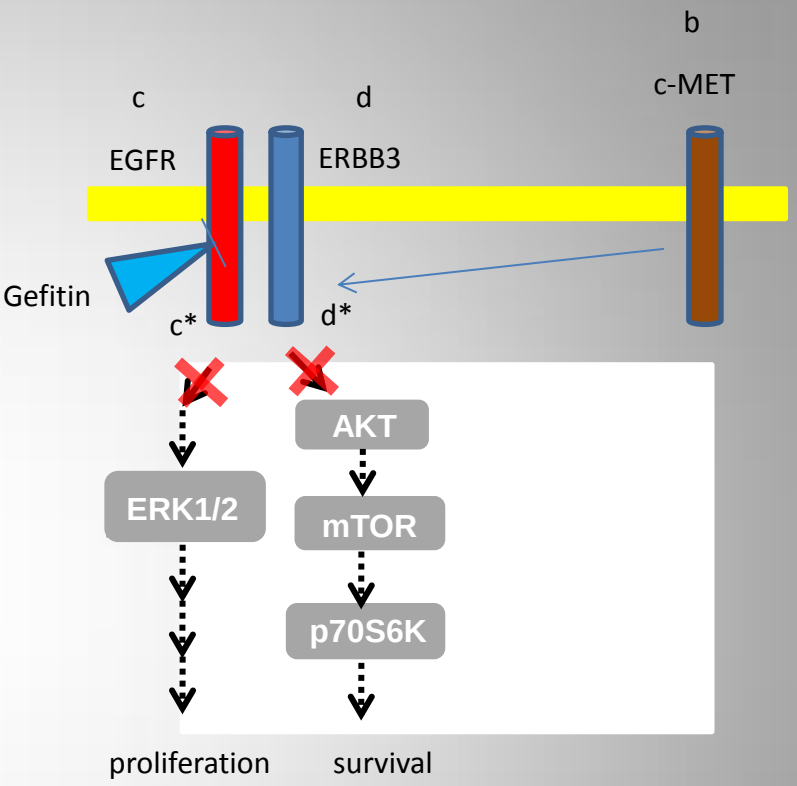
$$\frac{d}{dt}([A] + 2[P]) = 0$$ A - conservation

Drug Resistance - Quantitative Modeling

Level 1: Polymerization of EGFR, ERBB… malignant signal

Level 2: Gefitinib … suppresses downstream signal

Level 3: c-MET…phosphorylation repairing



signals

1. hierarchical

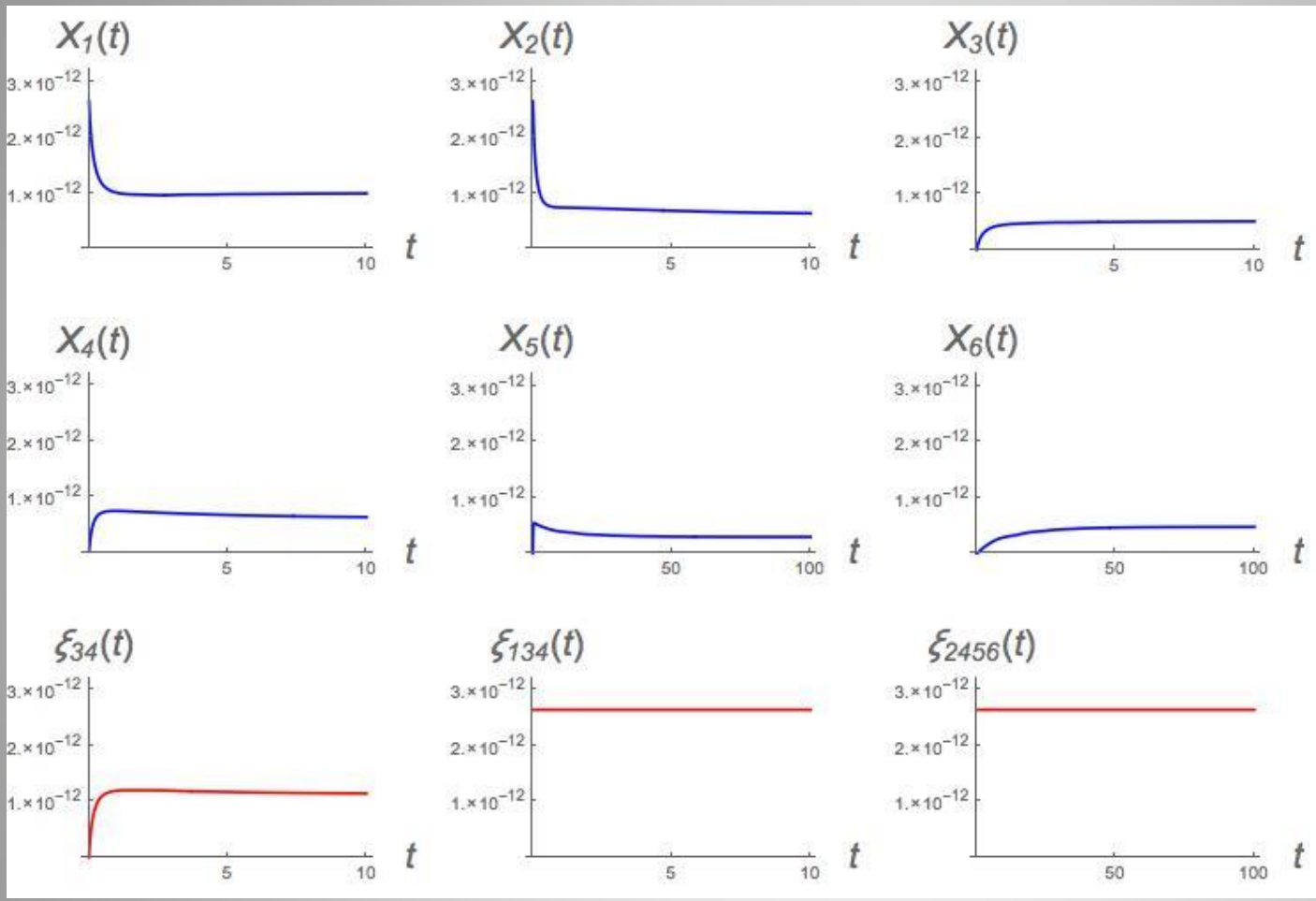
attachment
competitive

2. double scale

phosphorylation
catalytic differentiation
dimerization

through relaxation dynamics

simulations using experimental data



$k1+ = 3.8\times 10^{11}$, $k1- = 0.724$
その他の結合定数 $= 1 \times 10^{12}$
その他の解離定数 $= 1$
リン酸化定数 $= 4.5\times 10^{-2}$
脱リン酸化定数 $= 2.8\times 10^{-2}$

$X1(0) = X2(0) = 2.64 \times 10^{-12}$
$X3(0) = X4(0) = X5(0) = X6(0) = 0$

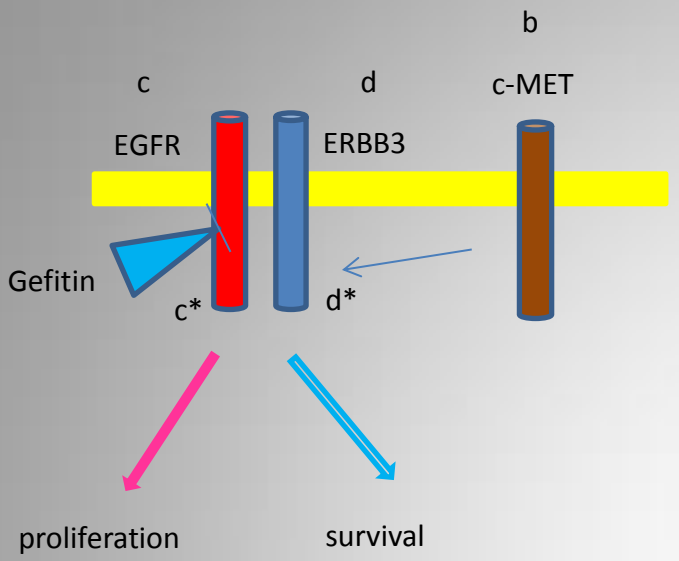
$\xi_{34} = X3 + X4$
$\xi_{134} = X1 + 2\,X3 + X4$
$\xi_{2456} = X2 + X4 + 2\,X5 + 2\,X6$

$X1(\infty) = 1.01253\times 10^{-12}$
$X2(\infty) = 5.44435\times 10^{-13}$
$X3(\infty) = 5.38095\times 10^{-13}$
$X4(\infty) = 5.51276\times 10^{-13}$
$X5(\infty) = 2.96393\times 10^{-13}$
$X6(\infty) = 4.75752\times 10^{-13}$
$\xi_{34}(\infty) = 1.08937\times 10^{-12}$
$\xi_{134}(\infty) = 2.64\times 10^{-12}$
$\xi_{2456}(\infty) = 2.64\times 10^{-12}$

initial value + homo-dimerization … EGFR
phosphorylation dephosphorylation … ERBB

initial vale EGFR → ERBB
other attachment detachment … dimension analysis

Summary



Events are appropriate!

membrane type receptor/proteinase complexes

→ downstream signaling → cell function

modeling (1)

attachment law → molecules → pathways

modeling (2)

dimerization → phosphorylation → signals

parametrization (1)

molar concentration
time scale → dimension analysis → reaction rates

parametrization (2) ⇕ equilibrium
attachment
phosphorylation

simulation ⟶ experiments