REACTION NETWORKS

Scales:

- Molecular (diffusion, "motors"; ions, charges, bonds, binding sites, conformation, energetics, single events…)

- Cellular (transport, transporters, chemotaxis; signal transduction, transcription/translation, regulation, metabolism)

- Tissue/organ (blood/lymph flow, muscles, pumps; regulation tissue growth/death, development)

- Whole individual (neurohormonal regulation, pharmacokinetics, pharmacodynamics, genetic variation, cancer, immunology, infection, …)

FOCUS: finite dim. system of coupled differential (and algebraic) equations

- Rate laws (elementary, mass action, approximate, empirical)

- State variables: concentrations, masses, (fraction occupied binding sites, voltages, …)

- Dependent variables (data): concentration, specific activity, flux, flow,… of selected species; linear combinations or ratios

- Independent variables ("design"):
  - time
  - temperature, pH, fixed conc.
  - experimental probes (initial conditions, input fluxes; constant flux input → steady state)

…but will limit the focus:

- no spatial terms/PDE models (may be approximated by compartments coupled with transport)
- no process noise
- no model misspecification (though discrimination among candidate models can be addressed)
- only "noise" (if any) is random measurement error for dependent variables
- large # molecules; well stirred

Today at 2pm Beckman Auditorium
Dan Gillespie
"Stochastic Chemical Kinetics"
http://bnmc.caltech.edu/Events/
(Markov process, chemical master equation, stochastic simulation, …)

EXAMPLES

a) $X_1 \xrightarrow{k_1} X_2$

$$\dot{[X_1]} = -k_1 \cdot [X_1]$$
$$\dot{[X_2]} = k_1 \cdot [X_1]$$

(henceforth drop [.] conc. notation)

b) $X_1 + X_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X_3$

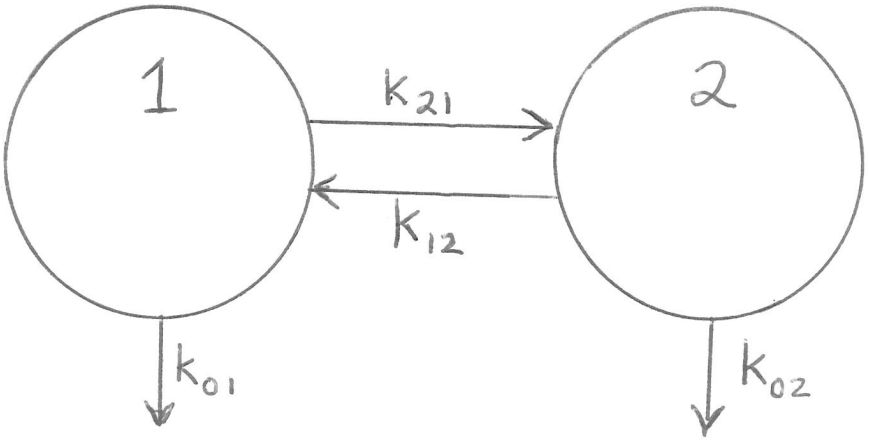
$$\dot{X}_1 = \dot{X}_2 = -k_1 \cdot X_1 \cdot X_2 + k_2 \cdot X_3$$

$$\dot{X}_3 = k_1 \cdot X_1 \cdot X_2 - k_2 \cdot X_3$$

Note: k_1 units [1/time]·[1/conc]
k_2 units [1/time]

$K_D = k_2 / k_1$ = dissociation constant
If $\dot{X}_1 = \dot{X}_2 = 0$, $X_1 \cdot X_2 / X_3 \equiv K_D$

c) compartmental models



q_i = mass of pool i ; $X_i = q_i / V_i$

$$\dot{q}_1 = -(k_{01} + k_{21})q_1 + k_{12}q_2$$

$$\dot{q}_2 = k_{21}q_1 - (k_{02} + k_{12})q_2$$

or $$\dot{\mathbf{q}} = \mathbf{K}\mathbf{q}$$

where $$(K)_{jj} = -\sum_{i \neq j} k_{ij}$$

d) "saturable" binding/kinetics

$$X_1 + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X_1R \xrightarrow{k_3} X_2 \ (\ldots + R)$$

- $R_{TOT} \equiv R + X_1R$ is total receptor/enzyme (often fixed)

- $\dot{X}_1 = -k_1 \cdot X_1 \cdot (R_{TOT} - X_1R) + k_2 \cdot X_1R$

- under small parameter assumptions (e.g., if $\varepsilon = R_{TOT}/X_1(0) << 1$) get Michaelis-Menten approximation ("outer solution" for long time scale)

$$X_1 \xrightarrow{Km,\,Vmax} X_2$$

where $\dot{X}_1 = -(Vmax/(Km + X_1)) \cdot X_1$

$Vmax = k_3 \cdot R_{TOT}$

$Km = (k_2 + k_3)/k_1$

e) examples of other approximate rate laws (empirical, lumping, rate-limiting,…)

- Hill equation

$$\dot{X} = - Vmax \cdot (X^n / (K^n_{50} + X^n))$$

- IP_3 = inositol 1,4,5 trisphosphate:

IP_3 induced Ca^{++} flux out of ER (endoplasmic reticulum, a subcellular "compartment")

$$= \alpha \cdot \left(IP_3/(K_1 + IP_3)\right)^3 \cdot [Ca^{++}]_{ER}$$

- S –systems (E. Voit)

$$\dot{X}_1 = \alpha X_3^{1.5} - \beta \cdot X_1^{0.5} \cdot X_3^{-1}$$

…

- various inhibition/stimulation schemes (feedback loops)

A mathematical model of metabolic insulin signaling pathways

Ahmad R. Sedaghat, Arthur Sherman and Michael J. Quon

AJP - Endo 283:1084-1101, 2002. First published Jul 2, 2002; doi:10.1152/ajpendo.00571.2001

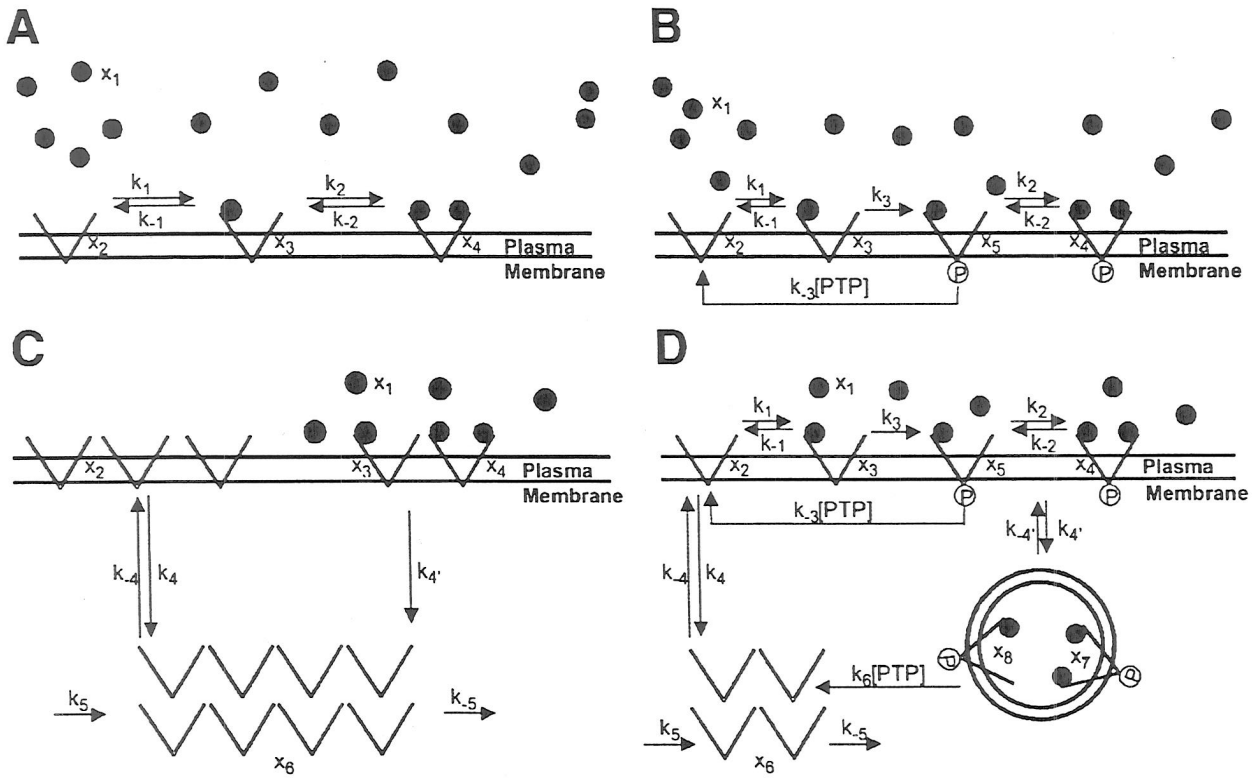


Fig. 1. Schematic of insulin receptor binding and life cycle subsystems. *A*: previously validated model of insulin binding kinetics (57). x_1, Free insulin concentration (system input); x_2, free receptor concentration; x_3, concentration of receptors with 1 molecule of insulin bound; x_4, concentration of receptors with 2 molecules of insulin bound; k_1 and k_{-1}, association and dissociation rate constants, respectively, for the first molecule of insulin to bind the receptor; k_2 and k_{-2}, association and dissociation rate constants, respectively, for the second molecule of insulin to bind the receptor. *B*: receptor binding subsystem extended to include receptor autophosphorylation and dephosphorylation. x_5, Concentration of once-bound phosphorylated receptors; x_4, redefined as concentration of twice-bound phosphorylated receptors; k_3, rate constant for receptor autophosphorylation; k_{-3}, rate constant for receptor dephosphorylation; [PTP], a multiplicative factor modulating k_{-3} that represents the relative activity of protein tyrosine phosphatases (PTPases) in the cell that dephosphorylate the insulin receptor. *C*: previously validated model of insulin receptor recycling (36). x_6, Concentrations of intracellular receptors; k_4, endocytosis rate constant for free receptors; k_{-4}, exocytosis rate constant; $k_{4'}$, endocytosis rate constant for bound receptors; k_5, zero order rate constant for receptor synthesis; k_{-5}, constant for receptor degradation. *D*: extension of insulin receptor binding and recycling subsystems that includes phosphorylated receptors. x_7 and x_8, concentration of twice-bound and once-bound intracellular phosphorylated receptors, respectively; $k_{-4'}$, exocytosis rate for twice-bound and once-bound intracellular phosphorylated receptors; k_6, dephosphorylation rate constant for intracellular receptors that is modulated by the multiplicative factor [PTP].

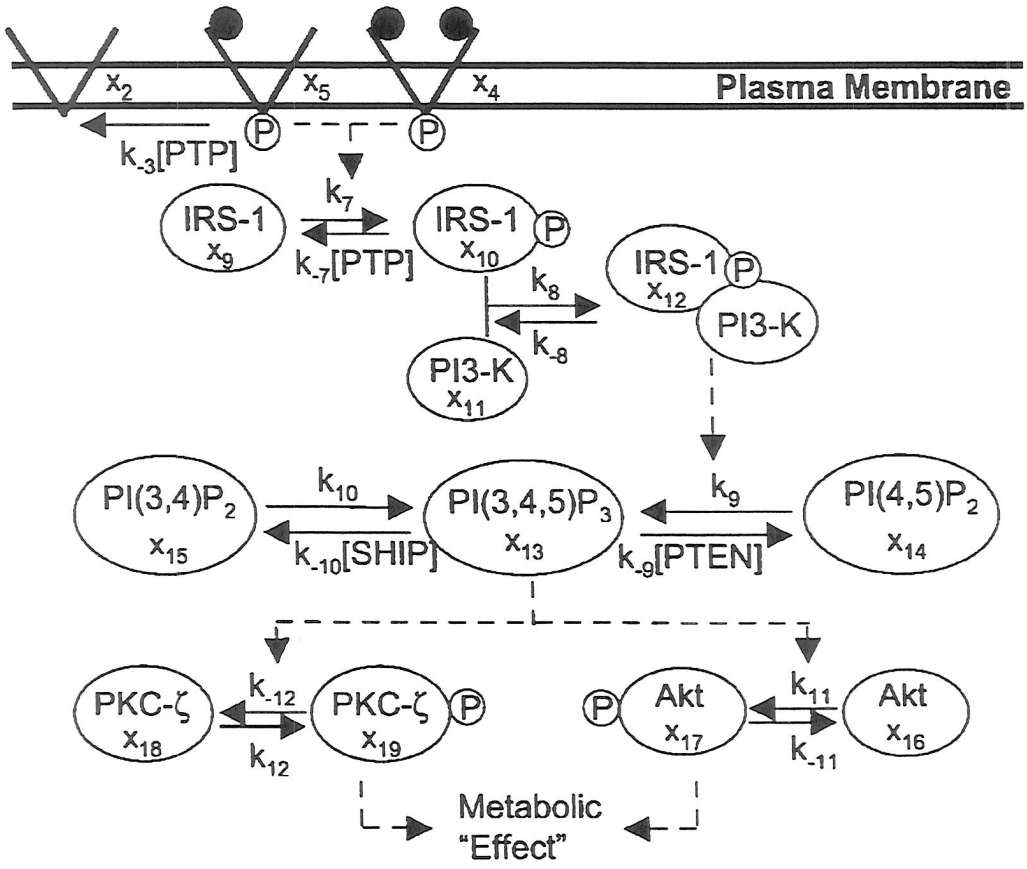


Fig. 2. Schematic of postreceptor signaling subsystem. x_9, Concentration of unphosphorylated insulin receptor substrate (IRS)-1; x_{10}, concentration of tyrosine-phosphorylated IRS-1; x_{11}, concentration of free phosphatidylinositol 3-kinase (PI 3-kinase; PI3-K); x_{12}, concentration of the phosphorylated IRS-1/activated PI 3-kinase complex; x_{13}, x_{14}, and x_{15}, percentages of various phosphoinositol lipids in the cell; x_{16} and x_{17}, percentages of unphosphorylated and phosphorylated Akt in the cell, respectively; x_{18} and x_{19}, percentages of unphosphorylated and phosphorylated protein kinase C (PKC)-ζ in the cell, respectively. The rate constants k_7 to k_{12} and k_{-7} to k_{-12} govern the conversion between state variables as indicated. [PTP] is a multiplicative factor modulating k_{-7} that represents the relative activity of PTPases in the cell that dephosphorylate IRS-1. [PTEN] and [SHIP] are multiplicative factors modulating k_{-9} and k_{-10}, respectively, that represent the relative activity of these lipid phosphatases in the cell. Arrows with solid lines indicate first-order reactions. Arrows with dashed lines indicate reactions where the value of a state variable influences the value of the rate constant.

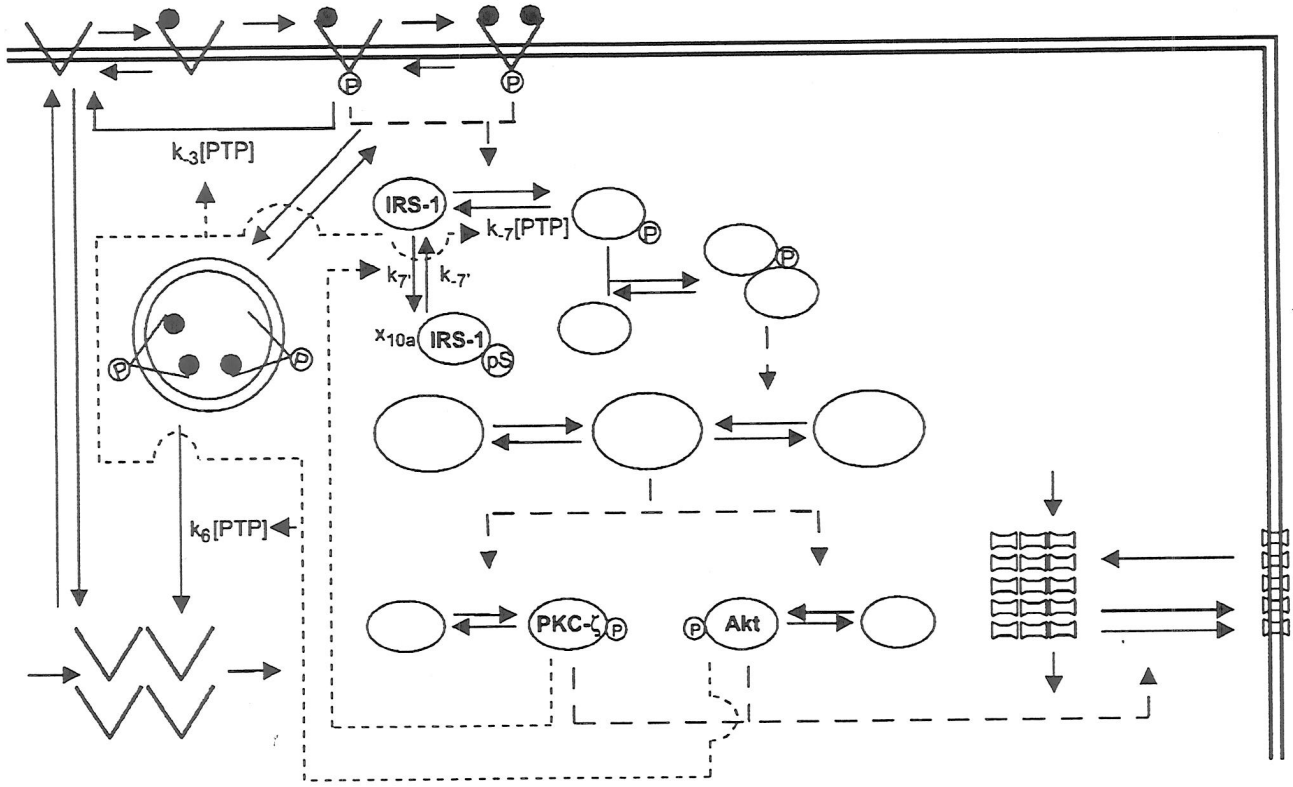


Fig. 5. Complete model of metabolic insulin signaling pathways with feedback. Identical to model shown in Fig. 4 except that new elements comprising positive and negative feedback pathways are indicated by dotted lines. PKC-ζ serine phosphorylates IRS-1 to create a negative feedback pathway, and Akt phosphorylates PTP1B to create a positive feedback pathway.

$$x_1 = \text{insulin input} \tag{6}$$

$$dx_2/dt = k_{-1}x_3 + k_{-3}[\text{PTP}]x_5 - k_1x_1x_2 + k_{-4}x_6 - k_4x_2 \tag{7}$$

$$dx_3/dt = k_1x_1x_2 - k_{-1}x_3 - k_3x_3 \tag{8}$$

$$dx_4/dt = k_2x_1x_5 - k_{-2}x_4 + k_{-4'}x_7 - k_{4'}x_4 \tag{9}$$

$$dx_5/dt = k_3x_3 + k_{-2}x_4 - k_2x_1x_5 - k_{-3}[\text{PTP}]x_5 + k_{-4'}x_8 - k_{4'}x_5 \tag{10}$$

$$dx_6/dt = k_5 - k_{-5}x_6 + k_6[\text{PTP}](x_7 + x_8) + k_4x_2 - k_{-4}x_6 \tag{11}$$

$$dx_7/dt = k_{4'}x_4 - k_{-4'}x_7 - k_6[\text{PTP}]x_7 \tag{12}$$

$$dx_8/dt = k_{4'}x_5 - k_{-4'}x_8 - k_6[\text{PTP}]x_8 \tag{13}$$

Differential equations governing phosphorylation of IRS-1 and subsequent formation of phosphorylated IRS-1/activated PI 3-kinase complex are

$$dx_9/dt = k_{-7}[\text{PTP}]x_{10} - k_7x_9(x_4 + x_5)/(IR_p) \tag{14}$$

$$dx_{10}/dt = k_7x_9(x_4 + x_5)/(\text{IR}_p) + k_{-8}x_{12} - (k_{-7}[\text{PTP}] + k_8x_{11})x_{10} \tag{15}$$

$$dx_{11}/dt = k_{-8}x_{12} - k_8x_{10}x_{11} \tag{16}$$

$$dx_{12}/dt = k_8x_{10}x_{11} - k_{-8}x_{12} \tag{17}$$

Activated PI 3-kinase converts the substrate phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] to the product PI(3,4,5)P_3. This is modeled as a linear function so that k_9, the rate constant for generation of PI(3,4,5)P_3, is dependent on x_{12}, the amount of activated PI 3-kinase (see APPENDIX B for detailed derivation). 5′-Lipid phosphatases such as SHIP2 convert PI(3,4,5)P_3 to phosphatidylinositol 3,4-bisphosphate [PI(3,4)P_2] (6), whereas 3′-lipid phosphatases such as PTEN convert PI(3,4,5)P_3 to PI(4,5)P_2 (45). The differential equations describing interconversion between these phosphatidylinositides are

$$dx_{13}/dt = k_9x_{14} + k_{10}x_{15} - (k_{-9}[\text{PTEN}] + k_{-10}[\text{SHIP}])x_{13} \tag{18}$$

$$dx_{14}/dt = k_{-9}[\text{PTEN}]x_{13} - k_9x_{14} \tag{19}$$

$$dx_{15}/dt = k_{-10}[\text{SHIP}]x_{13} - k_{10}x_{15} \tag{20}$$

... etc.

Model with Feedback

Additional state variables are as follows

x_{10a} = concentration of serine-phosphorylated IRS-1

Additional equations are as follows

$$dx_9/dt = k_{-7}[\text{PTP}]x_{10} - k_7 x_9(x_4 + x_5)/(\text{IR}_p) + k_{-7'}x_{10a} \quad k_7'[\text{PKC}]x_9 \text{ (updated)}$$

$$dx_{10a}/dt = k_7[\text{PKC}]x_9 - k_{-7'}x_{10a}$$

Additional initial conditions are as follows

$$x_{10a}(0) = 0$$

Additional parameters are as follows

$$k_{7'} = \ln(2)/2 \text{ min}^{-1}$$

$$k_{-7'} = k_{7'}\,[(2.5/7.45)(3.70 \times 10^{-13})]/[(6.27 \times 10^{-13}) - (2.5/7.45)(3.70 \times 10^{-13})]$$

✓ $[\text{PTP}] = 1.00\,[1 - 0.25(x_{17}/(100/11)]$ for $x_{17} \leq (400/11)$, otherwise $[\text{PTP}] = 0$ (updated)

$$\text{PI3K} = k_8(3.70 \times 10^{-13})(1 \times 10^{-13})/[k_8(3.70 \times 10^{-13}) + k_{-8}] \text{ (updated)}$$

✓ $[\text{PKC}] = V_{max}x_{19}(t - \tau)^n/[K_d^n + x_{19}(t - \tau)^n]$

$$V_{max} = 20$$

$$K_d = 12$$

$$n = 4$$

$$\tau = 1.5$$

APPENDIX A

Model without Feedback

State variables are as follows

x_1 = Insulin input
x_2 = Concentration of unbound surface insulin receptors
x_3 = Concentration of unphosphorylated once-bound surface receptors
x_4 = Concentration of phosphorylated twice-bound surface receptors
x_5 = Concentration of phosphorylated once-bound surface receptors
x_6 = Concentration of unbound unphosphorylated intracellular receptors
x_7 = Concentration of phosphorylated twice-bound intracellular receptors
x_8 = Concentration of phosphorylated once-bound intracellular receptors
x_9 = Concentration of unphosphorylated IRS-1
x_{10} = Concentration of tyrosine-phosphorylated IRS-1
x_{11} = Concentration of unactivated PI 3-kinase
x_{12} = Concentration of tyrosine-phosphorylated IRS-1/activated PI 3-kinase complex
x_{13} = Percentage of $PI(3,4,5)P_3$ out of the total lipid population
x_{14} = Percentage of $PI(4,5)P_2$ out of the total lipid population
x_{15} = Percentage of $PI(3,4)P_2$ out of the total lipid population
x_{16} = Percentage of unactivated Akt
x_{17} = Percentage of activated Akt
x_{18} = Percentage of unactivated PKC-ζ
x_{19} = Percentage of activated PKC-ζ
x_{20} = Percentage of intracellular GLUT4
x_{21} = Percentage of cell surface GLUT4

Equations are as follows

$$x_1 = \text{insulin input}$$
$$dx_2/dt = k_{-1}x_3 + k_{-3}[PTP]x_5 - k_1x_1x_2 + k_{-4}x_6 - k_4x_2$$
$$dx_3/dt = k_1x_1x_2 - k_{-1}x_3 - k_3x_3$$
$$dx_4/dt = k_2x_1x_5 - k_{-2}x_4 + k_{-4'}x_7 - k_{4'}x_4$$
$$dx_5/dt = k_3x_3 + k_{-2}x_4 - k_2x_1x_5 - k_{-3}[PTP]x_5 + k_{-4'}x_8 - k_{4'}x_5$$
$$dx_6/dt = k_5 - k_{-5}x_6 + k_6[PTP](x_7 + x_8) + k_4x_2 - k_{-4}x_6$$
$$dx_7/dt = k_{4'}x_4 - k_{-4'}x_7 - k_6[PTP]x_7$$
$$dx_8/dt = k_{4'}x_5 - k_{-4'}x_8 - k_6[PTP]x_8$$
$$dx_9/dt = k_{-7}[PTP]x_{10} - k_7x_9(x_4 + x_5)/(IR_p)$$
$$dx_{10}/dt = k_7x_9(x_4 + x_5)/(IR_p) + k_{-8}x_{12} - (k_{-7}[PTP] + k_8x_{11})x_{10}$$
$$dx_{11}/dt = k_{-8}x_{12} - k_8x_{10}x_{11}$$
$$dx_{12}/dt = k_8x_{10}x_{11} - k_{-8}x_{12}$$
$$dx_{13}/dt = k_9x_{14} + k_{10}x_{15} - (k_{-9}[PTEN] + k_{-10}[SHIP])x_{13}$$
$$dx_{14}/dt = k_{-9}[PTEN]x_{13} - k_9x_{14}$$
$$dx_{15}/dt = k_{-10}[SHIP]x_{13} - k_{10}x_{15}$$
$$dx_{16}/dt = k_{-11}x_{17} - k_{11}x_{16}$$
$$dx_{17}/dt = k_{11}x_{16} - k_{-11}x_{17}$$
$$dx_{18}/dt = k_{-12}x_{19} - k_{12}x_{18}$$
$$dx_{19}/dt = k_{12}x_{18} - k_{-12}x_{19}$$
$$dx_{20}/dt = k_{-13}x_{21} - (k_{13} + k_{13'})x_{20} + k_{14} - k_{-14}x_{20}$$
$$dx_{21}/dt = (k_{13} + k_{13'})x_{20} - k_{-13}x_{21}$$

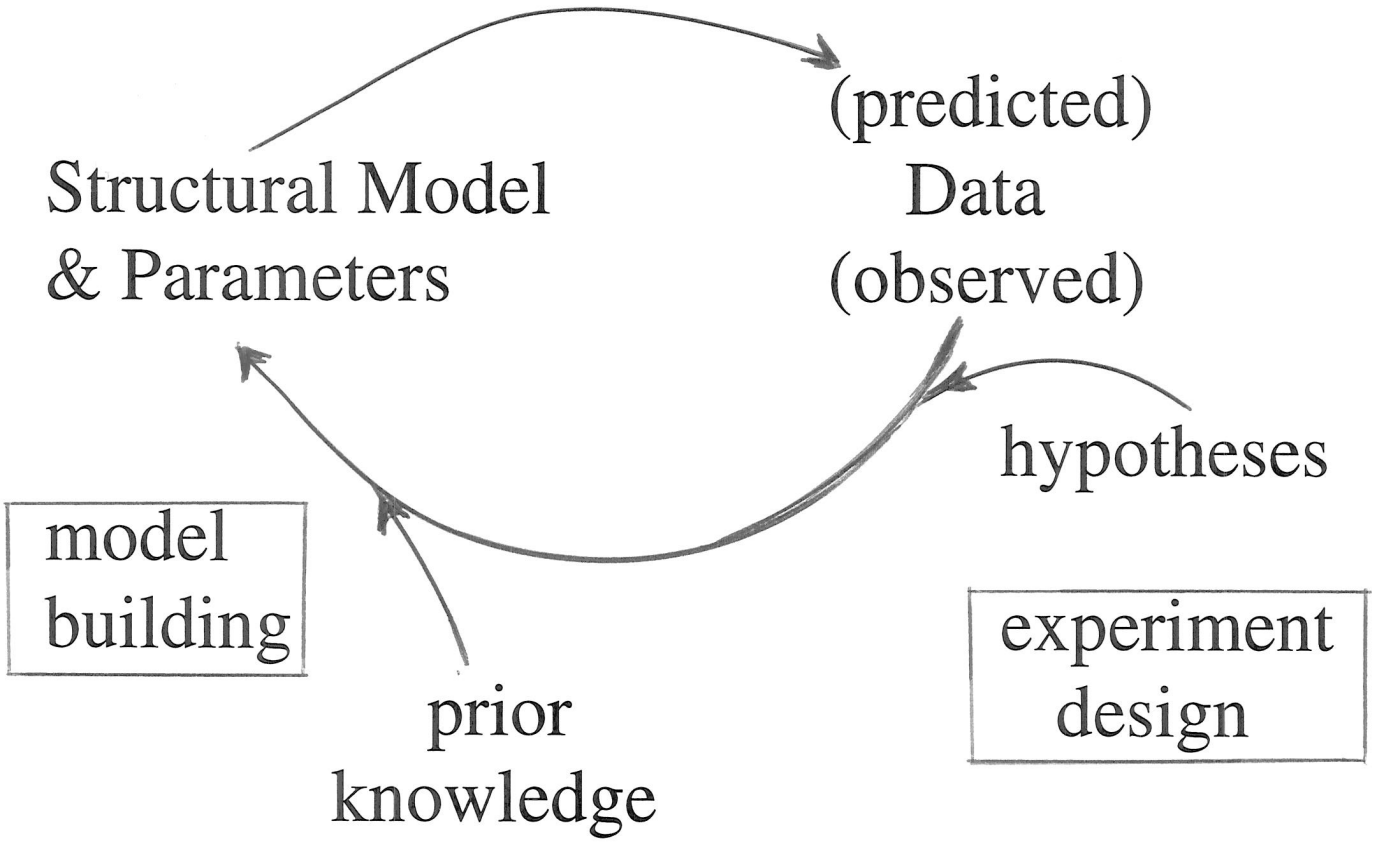
Initial conditions are as follows

$$x_1(0) = 0$$
$$x_2(0) = 9 \times 10^{-13}\ M$$
$$x_3(0) = 0$$
$$x_4(0) = 0$$
$$x_5(0) = 0$$
$$x_6(0) = 1 \times 10^{-13}\ M$$
$$x_7(0) = 0$$
$$x_8(0) = 0$$
$$x_9(0) = 1 \times 10^{-12}\ M$$
$$x_{10}(0) = 0$$
$$x_{11}(0) = 1 \times 10^{-13}\ M$$
$$x_{12}(0) = 0$$
$$x_{13}(0) = 0.31\%$$
$$x_{14}(0) = 99.4\%$$
$$x_{15}(0) = 0.29\%$$
$$x_{16}(0) = 100\%$$
$$x_{17}(0) = 0$$
$$x_{18}(0) = 100\%$$
$$x_{19}(0) = 0$$
$$x_{20}(0) = 96\%$$
$$x_{21}(0) = 4\%$$

Model parameters are as follows

$$k_1 = 6 \times 10^7\ M^{-1}\cdot min^{-1}$$
$$k_{-1} = 0.20\ min^{-1}$$
$$k_2 = k_1$$
$$k_{-2} = 100k_{-1}$$
$$k_3 = 2{,}500\ min^{-1}$$
$$k_{-3} = k_{-1}$$
$$k_4 = k_{-4}/9$$
$$k_{-4} = 0.003\ min^{-1}$$
$$k_{4'} = 2.1 \times 10^{-3}\cdot min^{-1}$$
$$k_{-4'} = 2.1 \times 10^{-4}\cdot min^{-1}$$
$$k_5 = 10k_{-5}\ M\cdot min^{-1} \text{ if } (x_6 + x_7 + x_8) > 1 \times 10^{-13}$$
$$= 60k_{-5}\ M\cdot min^{-1} \text{ if } (x_6 + x_7 + x_8) \le 1 \times 10^{-13}$$
$$k_{-5} = 1.67 \times 10^{-18}\ min^{-1}$$
$$k_6 = 0.461\ min^{-1}$$
$$k_7 = 4.16\ min^{-1}$$
$$k_{-7} = (2.5/7.45)k_7$$
$$k_8 = k_{-8}(5/70.775) \times 10^{12}$$
$$k_{-8} = 10\ min^{-1}$$
$$k_9 = (k_{9(stimulated)} - k_{9(basal)})(x_{12}/PI3K) + k_{9(basal)}$$
$$k_{9(stimulated)} = 1.39\ min^{-1}$$
$$k_{-9} = (94/3.1)k_{9(stimulated)}$$
$$k_{9(basal)} = (0.31/99.4)k_{-9}$$
$$k_{10} = (3.1/2.9)k_{-10}$$
$$k_{-10} = 2.77\ min^{-1}$$
$$k_{11} = (0.1k_{-11})(x_{13} - 0.31)/(3.10 - 0.31)$$
$$k_{-11} = 10 \ln (2)\ min^{-1}$$
$$k_{12} = (0.1k_{-12})(x_{13} - 0.31)/(3.10 - 0.31)$$
$$k_{-12} = 10 \ln (2)\ min^{-1}$$
$$k_{-13} = 0.167\ min^{-1}$$
$$k_{13} = (4/96)k_{-13}$$
$$k_{13'} = [(40/60) - (4/96)]k_{-13}\cdot(\text{Effect})$$
$$k_{14} = 96k_{-14}$$
$$k_{-14} = 0.001155\ min^{-1}$$
$$\text{effect} = (0.2x_{17} + 0.8x_{19})/(AP_{equil})$$
$$IR_p = 8.97 \times 10^{-13}\ M$$
$$[SHIP] = 1.00$$
$$[PTEN] = 1.00$$
$$[PTP] = 1.00$$
$$AP_{equil} = 100/11$$
$$PI3K = 5 \times 10^{-15}\ M$$

"forward problem"
(i.e., simulation)



"inverse problem"

- parameter estimation
- model verification/testing
- model discrimination
- ? parameter "optimization"
- ? reverse engineering

Structural (or *a priori*) Identifiability addresses the question of a unique inverse

Given:

- Specified experiment design
  - design space *S* (e.g., range of times can sample)
  - specified input(s)
  - set of dependent variables ($\mathbf{y}(t)$) to be observed, without error, over *S*

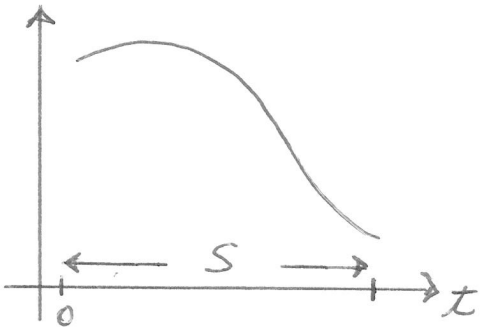
- Structural model $\mathbf{f}$, with unknown parameter vector $\theta \in \Theta \subset R^p$, that relates the design to observed data:

$$\mathbf{y}(t) = \mathbf{f}(t; \theta) \quad (+ \text{ no error})$$

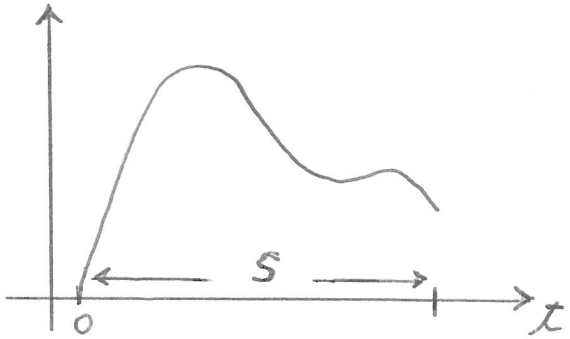
Question: Is there a unique choice of θ for every possible observed data set $\mathbf{y}$?
(i.e., is inverse map $\mathbf{y} \rightarrow \theta$ 1-to-1 or 1-to-many)

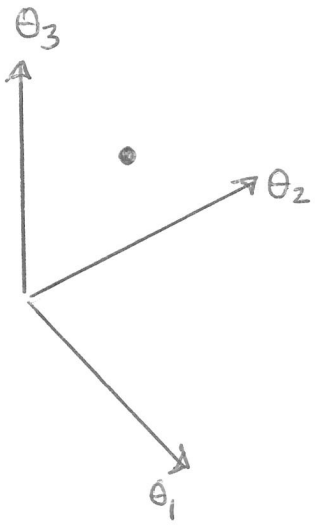
illustration:

$y_1(t) = X_1(t)$

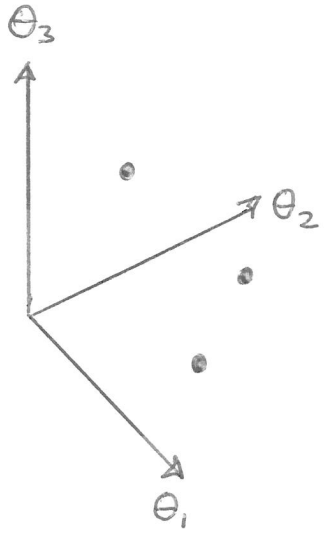


$y_2(t) = X_2(t) + X_3(t)$

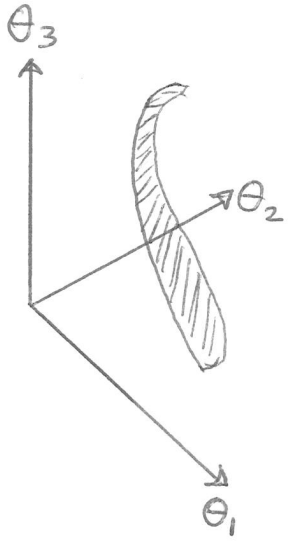




unique:
globally identifiable



separable:
locally identifiable



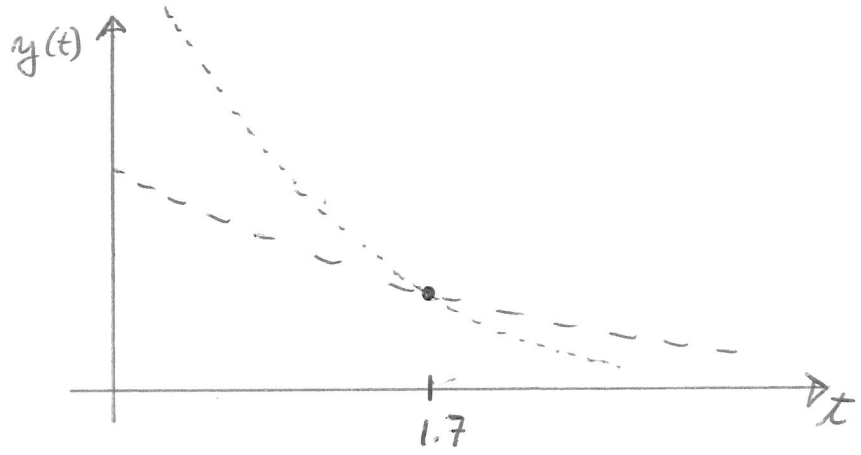
unidentifiable

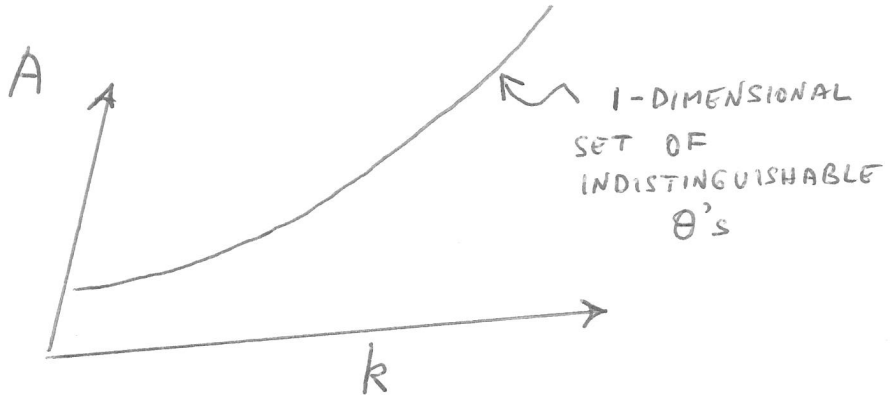
output indistinguishable manifold

trivial example: unidentifiable

$$y(t) = A \exp(-k \cdot t) \qquad \theta = (A, k)$$

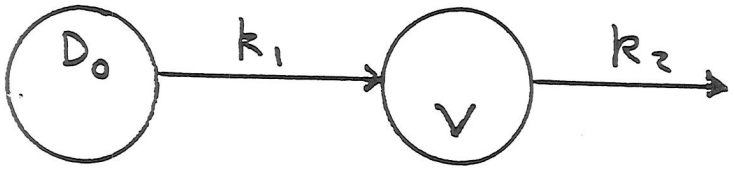
but $S = \{1.7 \text{ only}\}$





Note: *a priori* $k \geq 0$, which implies A is bounded below. If have upper bound for k then A would be "interval identifiable."

Example: local identifiability



y = CONCENTRATION IN CENTRAL POOL

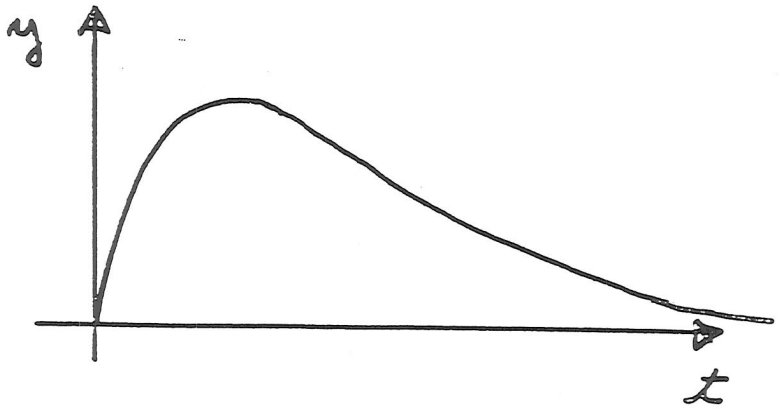
$$= \frac{D_0}{V} \frac{k_1}{k_1 - k_2} \left(e^{-k_2 t} - e^{-k_1 t} \right)$$

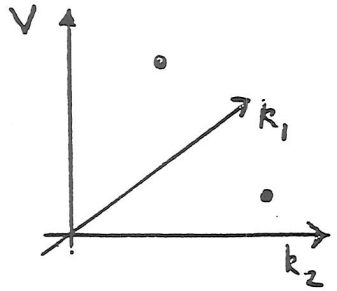
MODEL : ABOVE

CHOICE OF IND. VARIABLE : $0 \leq t < \infty$

ONLY CENTRAL POOL

$$\underline{\theta} = (k_1, k_2, V)$$



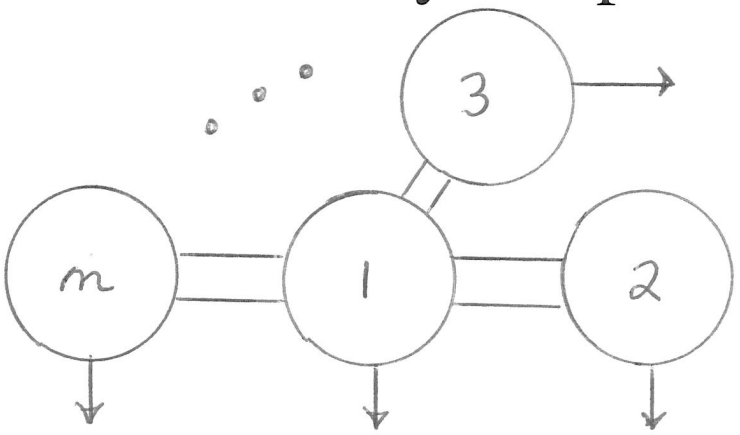


: 2 CHOICES OF $\underline{\theta}$

$$\theta = (k_1, k_2, V)$$

$$\theta' = \left(k_2, k_1, \frac{V k_2}{k_1}\right)$$

Example: mammillary comp. model



Input: known bolus dose into pool 1
Sample concentration of pool 1

$$y(t) = q_1(t)/V_1 = \sum_{i=1}^{n} A_i \exp(\lambda_i t)$$

(*a priori*: if k_{jj} distinct, j=2,…n, then

$$A_i > 0 \ , \lambda_i < \lambda_{i+1} \leqslant 0)$$

2n "macroparameters" $\{A_i, \lambda_i\}$ <u>identifiable</u>

3n-1 "microparameters" $\{k_{ij}, V_1\}$ <u>unident.</u>

2n <u>identifiable</u> parameter combinations:
$\{k_{11},\ldots,k_{nn}, k_{12}\cdot k_{21},\ldots k_{1n}\cdot k_{n1}, V_1\}$ which implies here that micros are interval ident.

Systematic Approaches to Identifiability

a) dimensionality arguments

b) linear systems – convert problem to the solvability of a finite system of nonlinear algebraic (polynomial) equations. (Computer Algebra)

- Laplace transforms
- finite number of $y(0^+)$, $y'(0^+)$, $y''(0^+)$, … (Markov matrices)
- transfer function topological method
- similarity transformation method (count all similarity transformations rendering it output indistinguishable)

c) nonlinear systems – system of equations may be infinite, greater dependence on initial conditions and type of input, etc. See Audoly, Chapman, Chappell, Saccomani references

d) numerical approach:

- pick nominal value θ^*

- generate $\mathbf{y_i} = \mathbf{f}(t_i, \theta^*)$, i=1,…,N
  with t_i sampling *S*

- idea is to evaluate in nbd of θ^*

$$Q(\theta) = \Sigma_i \, (\mathbf{y_i} - \mathbf{f}(t_i, \theta))' W_i (\mathbf{y_i} - \mathbf{f}(t_i, \theta))$$

(e.g., W_i may be a diag., positive matrix).
If system is locally identifiable, then $Q(\theta)$ will have a unique minimum (zero) at θ^*

- Compute PxP "information matrix"

$$M(\theta^*) = \Sigma_i \, M(t_i; \theta) \Big|_{\theta = \theta^*}$$

where $M(t_i; \theta) = (\partial \mathbf{y_i}/\partial\theta)' \, W_i \, (\partial \mathbf{y_i}/\partial\theta)$

- M full rank → locally identifiable

Note need in previous method for computing model sensitivities ($\partial y/\partial \theta$). Also used for real data (i.e., in presence of measurement noise) for

- numerical search for least squares estimate $\hat{\theta}$
- asymptotic covariance matrix for estimate $\hat{\theta}$

($COV(\hat{\theta})$ proportional to M^{-1})

Methods for computing sensitivities:

- one-sided or two-sided differences
- secant approximations (BMDPAR)
- augment state differential equations with sensitivity equations ($\partial \dot{y}/\partial \theta$).

Options if Model is Unidentifiable

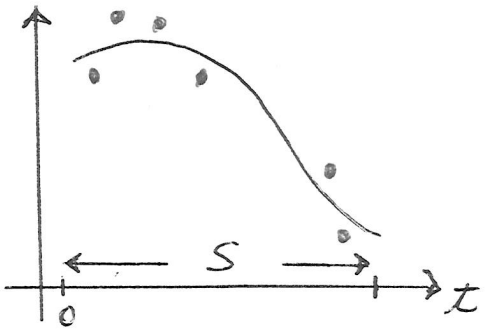
- search for improved design (augment sampled outputs and/or experimental probes)

- evaluate identifiable parameter combinations (e.g., W3MAMCAT www.biocyb.cs.ucla.edu/biocybmodeling.html)
  - may find useful subset of parameters that are identifiable
  - may provide interval identifiability

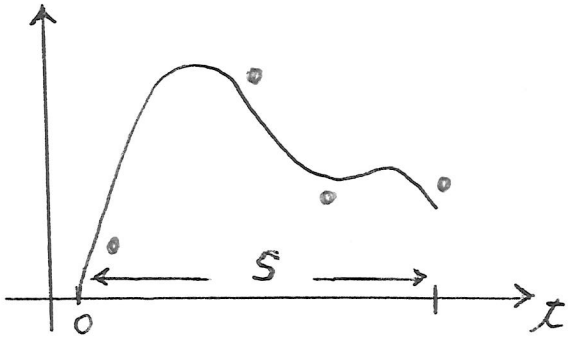
- augment with external information (e.g., Bayesian priors)

illustration:

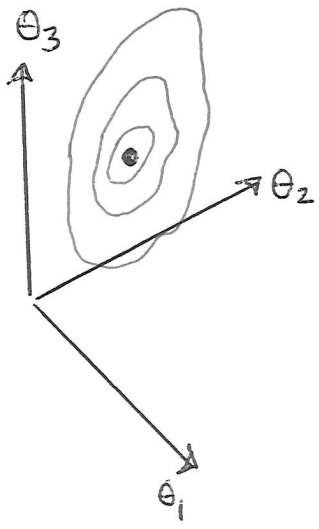
$y_1(t) = X_1(t)$

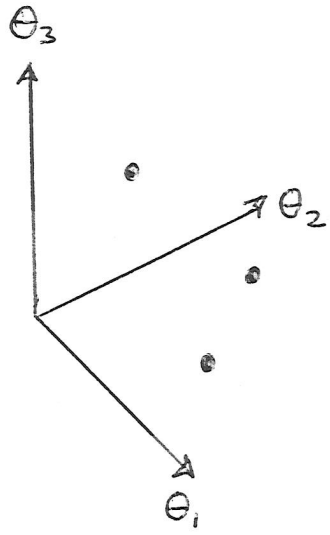


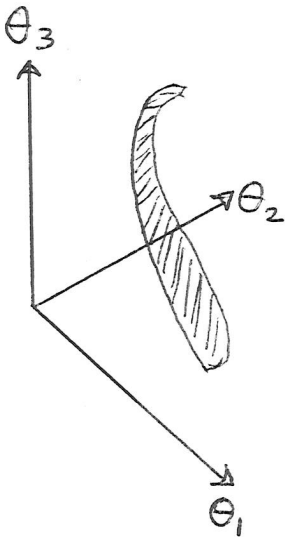
$y_2(t) = X_2(t) + X_3(t)$



FINITE, NOISY DATA







unique:
globally identifiable

separable:
locally identifiable

unidentifiable

output indistinguishable manifold

Even if model is identifiable, for real data must be concerned about "numerical identifiability" i.e., how presence of data noise affects precision of estimates:

$$\mathbf{y}(t) = \mathbf{f}(t; \theta) \quad + \text{ error}$$

- confidence regions for θ (or Bayesian posterior credibility regions) depend critically on design and model of measurement error (e.g., additive vs multiplicative error; error distribution; variance as a function of signal)

- may find subsets of parameters or functions of parameters estimated with adequate precision

- optimal experiment design may improve estimation precision (e.g., choose design $\{t_1,\ldots,t_N\}$ that minimizes $\det(\mathrm{COV}(\hat{\theta}))$.

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