PROBLEM 5: MODELING CONTROL OF HIV INFECTION THROUGH STRUCTURED TREATMENT INTERRUPTIONS

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Highly Active Anti-Retroviral Therapy (HAART) of HIV infection has significantly reduced morbidity and mortality in developed countries. However, since these treatments can cause side effects and require strict adherence to treatment protocol, questions about whether or not treatment can be interrupted or discontinued with control of infection maintained by the host immune system remain to be answered. We examined a model incorporating structured treatment interruptions (STI) in order to suggest a treatment protocol for experiements to be performed at Merck. We suggest both which compartments should be collected as well as a timing schedule for treatment.

OUTLINE

- Model
- Sensitivity Analysis

    -Compartments

    -Parameters

    -Time schedule

- Inverse Problem

Modification of Wodarz-Nowak Model for HIV Infection Dynamics

$$\begin{aligned}
\dot{X} &= \lambda - d\,X - \beta\,[1 - f\,u(t)]\,XV \\
\dot{Y} &= \beta\,[1 - f\,u(t)]\,XV - a\,Y - p\,YZ \\
\dot{W} &= c\,XYW - cq\,YW - bW \\
\dot{Z} &= cq\,YW - h\,Z \\
\dot{V} &= k\,Y - \mu\,V
\end{aligned}$$

X = Uninfected T helper cells

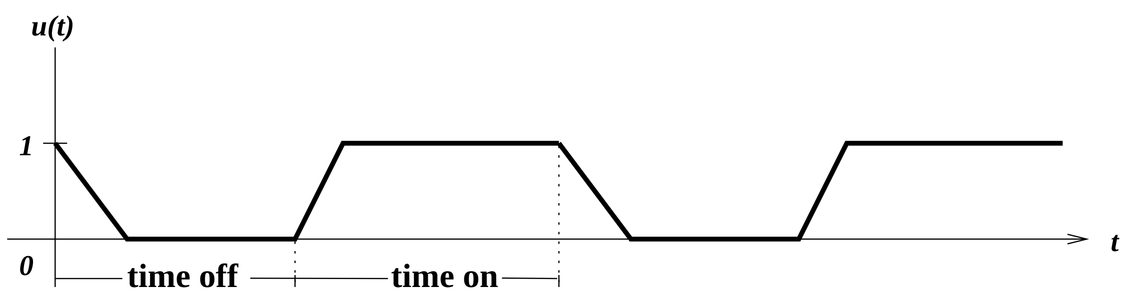
Y = Infected T helper cells

W = Immune Precursor Cytotoxic T Lymphocyte

Z = Immune Effector Cytotoxic T Lymphocyte

V = Free Virus

This is a modified version of the Wodarz-Nowak model for HIV infection dynamics. The modification involves the addition of an extra compartment, V, to represent the viral load present as a difference of a linear birthrate dependent on the number of infected cells and a deathrate of the short-lived virus. This model has two stable equilibria. One represents control of the virus by immune response and the other represents destruction of the immune response by virus. System parameters and initial conditions determine which equilibrium is realized.


u(t)
1
0
t
time off
time on

This shows treatment schedule during STI. Notice the time allotted for the drug to clear the body and ramp back up again. Values of $u(t)$range from 0 to 1. Explain values for δ t.

MODEL

$$
\begin{aligned}
\mathbf{z} &= [X, Y, W, Z, V] \text{ Model Compartments}\\
\mathbf{q} &= [\lambda, d, \beta, a, p, c, q, b, h, k, \mu, f] \text{ Parameters}\\
\log \hat{\mathbf{z}}_{\mathbf{i}} &= \log \mathbf{z}_{\mathbf{i}} + \eta * N[0,1] \text{ Simulated Data}\\
C &= \text{ Observation matrix}
\end{aligned}
$$

INVERSE PROBLEM

$$
\min_{\mathbf{q} \in Q_{ad}} J(\mathbf{q}) = \frac{\sum_i |\log(C * \mathbf{z}(t_i, \mathbf{q})) - \log(C * \hat{\mathbf{z}}_{\mathbf{i}})|^2}{\sigma_i^2} \text{Cost Function}
$$

SENSITIVITY

$$
\begin{aligned}
\frac{\partial J}{\partial \mathbf{q}}(\mathbf{q_0}) &= \sum_i 2 \frac{\log(C * \mathbf{z}(t_i, \mathbf{q_0})) - \log(C * \hat{\mathbf{z}}_{\mathbf{i}})}{\sigma_i^2} \cdot \frac{C^T}{C * \mathbf{z}(t_i, \mathbf{q_0})} \left(\frac{\partial \mathbf{z}}{\partial \mathbf{q}}(t_i, \mathbf{q_0}) \right)\\
\frac{\partial \mathbf{z}}{\partial \mathbf{q}} &= \text{ Sensitivity Matrix}
\end{aligned}
$$

Sensitivity analysis: Explain cost function

- Many goals: You have your model and want to eventually get real data. For the time being, you simulate data with some scatter. This helps determine which parameters might be most sensitive, that is, most important to estimate correctly when you eventually solve the inverse problem. Determine which parameters play a significant role in dynamics

- Also have C matrix that helps determine which compartments are most important to collect. It is expensive and difficult to collect data for all compartments, but if two compartments are combined, there is a significant decrease in cost. For example, you might collect x and y together or W and Z together.

- The inverse problem to eventually solve involves choosing the best values for parameters, which will minimize $J(q)$. $z(t_i, q)$ is found for given values of q by solving the original ODE. We used a stiff solver 15s.

- $\frac{\partial J}{\partial q}(q_0)$ will help determine which parameters are most sensitive. (heather)

- $\frac{\partial z}{\partial q}$, the sensitivity matrix informs which times would be most criticcal for collecting data by examining when various compartments are most sensitive to various parameters. (ed)

Observables: $C\,\mathbf{z}$

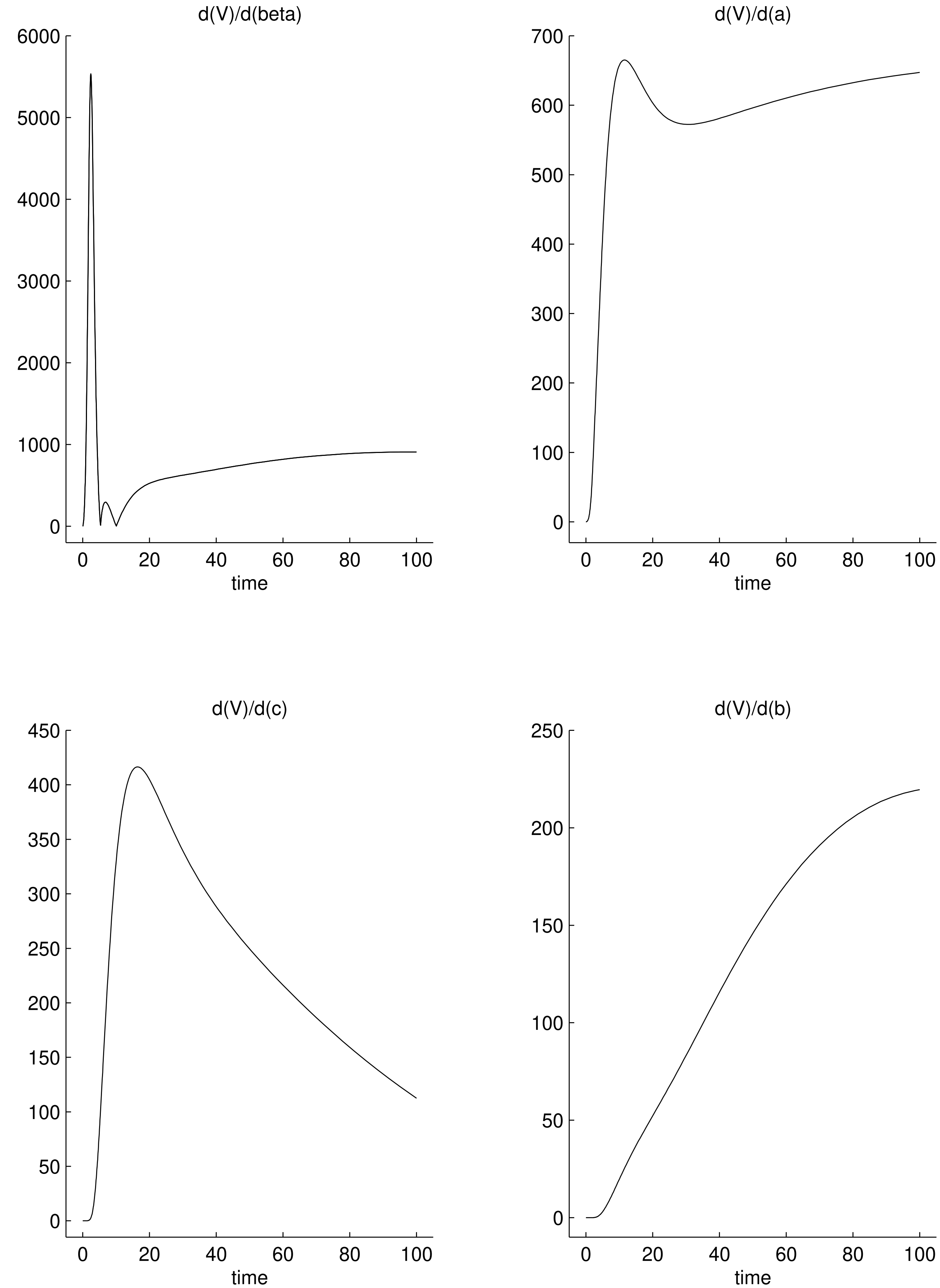
$$
\begin{aligned}
C_1\,\mathbf{z} &= \begin{pmatrix} X \\ Y \\ W \\ Z \\ V \end{pmatrix} \\
C_2\,\mathbf{z} &= \begin{pmatrix} X \\ Y \\ W + Z \\ V \end{pmatrix} \\
C_3\,\mathbf{z} &= \begin{pmatrix} X + Y \\ W + Z \\ V \end{pmatrix} \\
C_4\,\mathbf{z} &= \begin{pmatrix} X + Y \\ W + Z \end{pmatrix} \\
C_5\,\mathbf{z} &= \begin{pmatrix} X \\ Y \\ V \end{pmatrix} \\
C_6\,\mathbf{z} &= \begin{pmatrix} V \end{pmatrix}
\end{aligned}
$$

Some compartments are expensive to measure individually, but less expensive to measure together. Incorporating a matrix representing combinations of compartments in the cost function helped to determine if combining measurements of compartments would be feasible.

dJ/dq plots: treatment and no treatment?

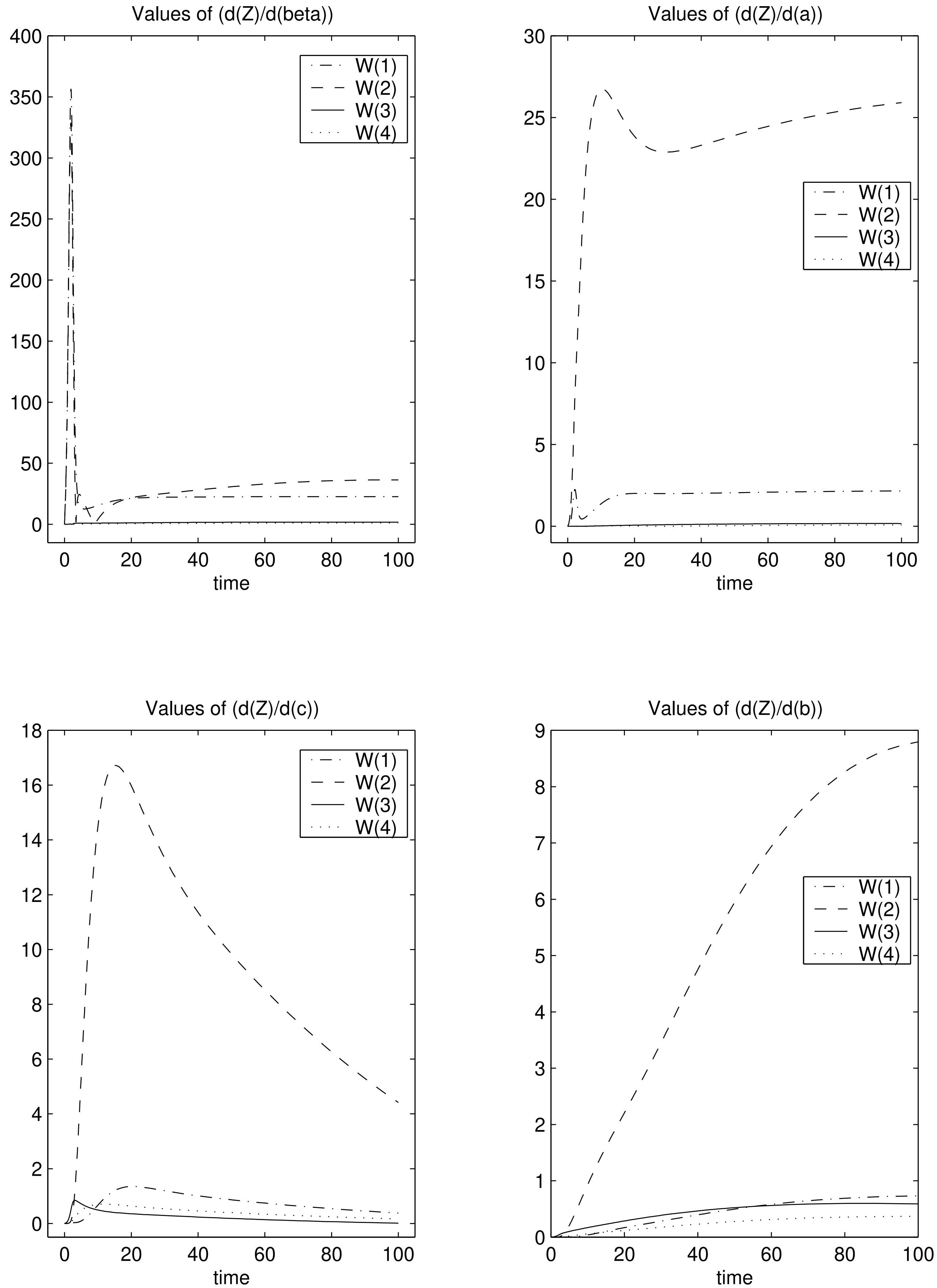
dJ/dq plots: treatment and no treatment?

Sensitivity of V over time, no treatment


d(V)/d(beta)
6000
5000
4000
3000
2000
1000
0
0 20 40 60 80 100
time
d(V)/d(a)
700
600
500
400
300
200
100
0
0 20 40 60 80 100
time
d(V)/d(c)
450
400
350
300
250
200
150
100
50
0
0 20 40 60 80 100
time
d(V)/d(b)
250
200
150
100
50
0
0 20 40 60 80 100
time

Use sensitivity matrix to determine time schedule for measurement of z

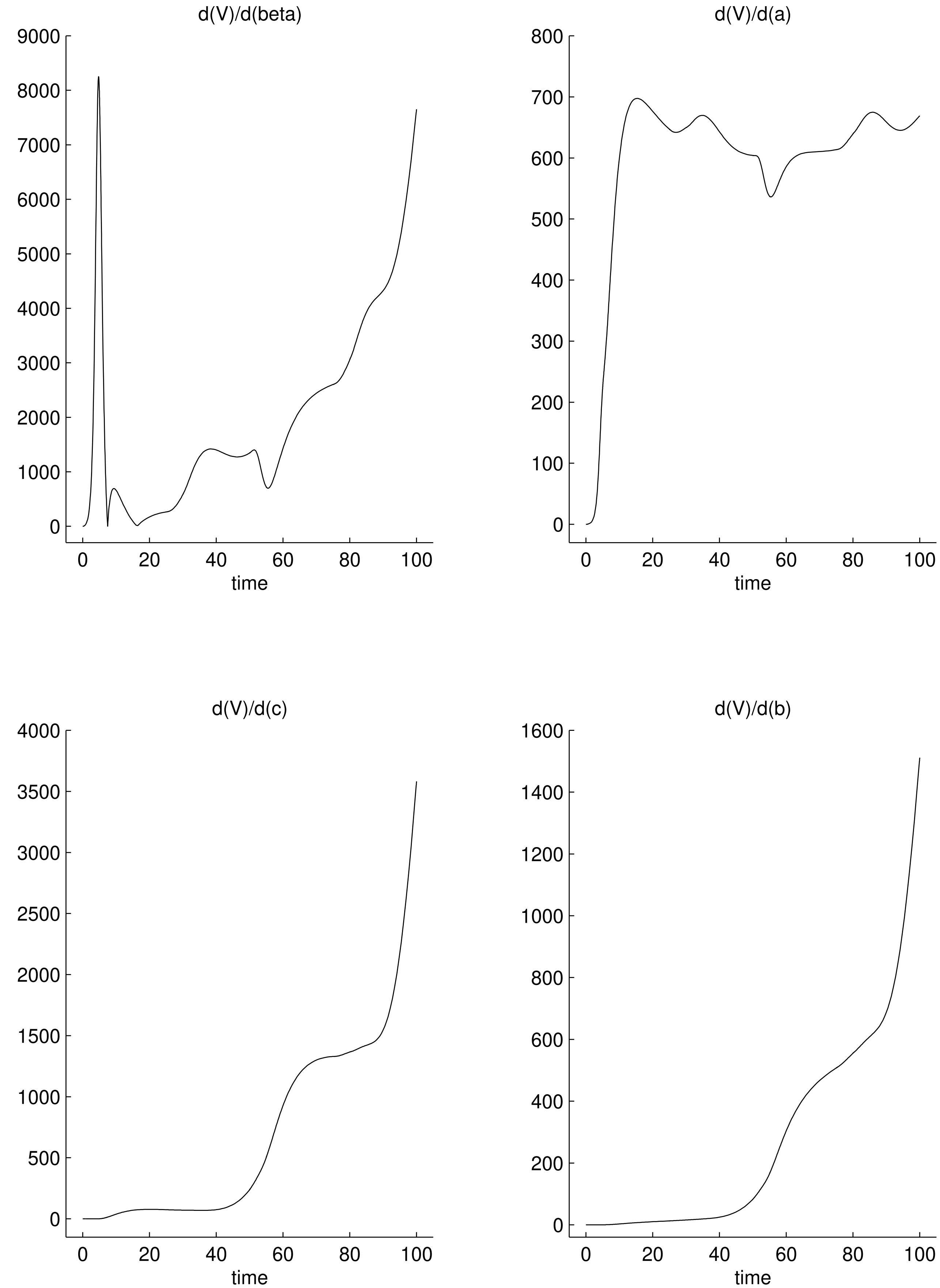
Sensitivity of z over time, no treatment



Values of (d(Z)/d(beta))
Values of (d(Z)/d(a))
Values of (d(Z)/d(c))
Values of (d(Z)/d(b))
W(1)
W(2)
W(3)
W(4)
time

Ditto

Sensitivity of V over time, periodic treatment


d(V)/d(beta)
d(V)/d(a)
d(V)/d(c)
d(V)/d(b)
time
time
time
time

Same thing under treatment.

Conclusion/Questions for Future Consideration

- We solved the inverse problem for fictional data

- The model seems to perform well for treatment or no treatment

- Next step is to develop experimental protocol

- Measure $X + Y$, $W + Z$, V

- Try to estimate parameters β, c, a, b, and f with treatment

- Investigate timing schedule based on sensitivity matrix

- Solve inverse problem with real data

see slide