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Introducing Simulation-Based Design to Biological Engineers

Contents

- Design and Computing (Generic and Bio specific)
- Case study in research
- Case studies in instruction
- State of adoption and Challenges

Design always involved computing

LOGARITHMS, BASE 10 $\log_{10}x$ or lg x

x	0	1	2	3	4	5	6	7	8	9	ADD 1	2	3	4	5	6	7	8	9
10	.0000	0043	0086	0128	0170						4	8	13	17	21	25	29	34	38
						0212	0253	0294	0334	0374	4	8	12	16	20	24	28	32	36
11	.0414	0453	0492	0531	0569						4	8	12	16	19	23	27	31	35
						0607	0645	0682	0719	0755	4	7	11	15	19	22	26	30	33
12	.0792	0828	0864	0899	0934						4	7	11	14	18	21	25	28	32
						0969	1004	1038	1072	1106	3	7	10	14	17	20	24	27	31
13	.1139	1173	1206	1239	1271						3	7	10	13	16	20	23	26	30
						1303	1335	1367	1399	1430	3	6	10	13	16	19	22	26	29
14	.1461	1492	1523	1553	1584	1614	1644	1673	1703	1732	3	6	9	12	15	18	21	24	27
15	.1761	1790	1818	1847	1875	1903	1931	1959	1987	2014	3	6	8	11	14	17	20	22	25
16	.2041	2068	2095	2122	2148	2175	2201	2227	2253	2279	3	5	8	10	13	16	18	21	23
17	.2304	2330	2355	2380	2405	2430	2455	2480	2504	2529	2	5	7	10	12	15	17	20	22
18	.2553	2577	2601	2625	2648	2672	2695	2718	2742	2765	2	5	7	10	12	14	17	19	22
19	.2788	2810	2833	2856	2878	2900	2923	2945	2967	2989	2	4	6	9	11	13	15	18	20
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22	.3424	3444	3464	3483	3502	3522	3541	3560	3579	3598	2	4	6	8	10	11	13	15	17
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24	.3802	3820	3838	3856	3874	3892	3909	3927	3945	3962	2	4	5	7	9	11	13	14	16
25	.3979	3997	4014	4031	4048	4065	4082	4099	4116	4133	2	3	5	7	9	10	12	14	15
26	.4150	4166	4183	4200	4216	4232	4249	4265	4281	4298	2	3	5	6	8	10	11	13	14
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28	.4472	4487	4502	4518	4533	4548	4564	4579	4594	4609	2	3	5	6	8	9	11	12	14
29	.4624	4639	4654	4669	4683	4698	4713	4728	4742	4757	1	3	4	6	7	9	10	12	13
30	.4771	4786	4800	4814	4829	4843	4857	4871	4886	4900	1	3	4	6	7	8	10	11	13
31	.4914	4928	4942	4955	4969	4983	4997	5011	5024	5038	1	3	4	6	7	8	10	11	13
32	.5051	5065	5079	5092	5105	5119	5132	5145	5159	5172	1	3	4	5	7	8	9	10	12
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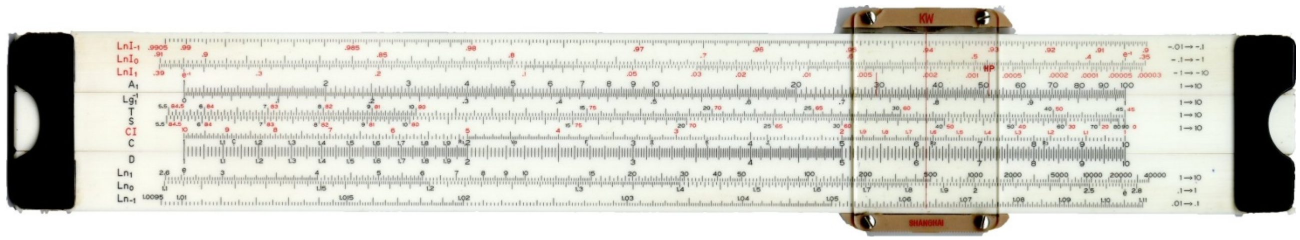
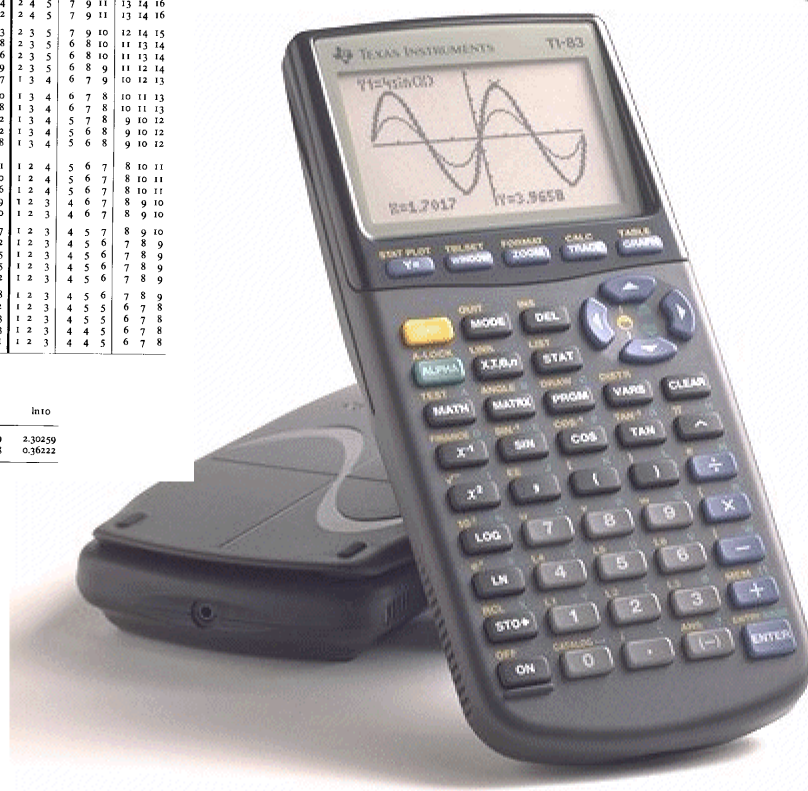
35	.5441	5453	5465	5478	5490	5502	5514	5527	5539	5551	1	2	4	5	6	7	8	10	11
36	.5563	5575	5587	5599	5611	5623	5635	5647	5658	5670	1	2	4	5	6	7	8	10	11
37	.5682	5694	5705	5717	5729	5740	5752	5763	5775	5786	1	2	4	5	6	7	8	10	11
38	.5798	5809	5821	5832	5843	5855	5866	5877	5888	5899	1	2	3	4	6	7	8	9	10
39	.5911	5922	5933	5944	5955	5966	5977	5988	5999	6010	1	2	3	4	6	7	8	9	10
40	.6021	6031	6042	6053	6064	6075	6085	6096	6107	6117	1	2	3	4	5	7	8	9	10
41	.6128	6138	6149	6160	6170	6180	6191	6201	6212	6222	1	2	3	4	5	6	7	8	9
42	.6232	6243	6253	6263	6274	6284	6294	6304	6314	6325	1	2	3	4	5	6	7	8	9
43	.6335	6345	6355	6365	6375	6385	6395	6405	6415	6425	1	2	3	4	5	6	7	8	9
44	.6435	6444	6454	6464	6474	6484	6493	6503	6513	6522	1	2	3	4	5	6	7	8	9
45	.6532	6542	6551	6561	6571	6580	6590	6599	6609	6618	1	2	3	4	5	6	7	8	9
46	.6628	6637	6646	6656	6665	6675	6684	6693	6702	6712	1	2	3	4	5	5	6	7	8
47	.6721	6730	6739	6749	6758	6767	6776	6785	6794	6803	1	2	3	4	5	5	6	7	8
48	.6812	6821	6830	6839	6848	6857	6866	6875	6884	6893	1	2	3	4	4	5	6	7	8
49	.6902	6911	6920	6928	6937	6946	6955	6964	6972	6981	1	2	3	4	4	5	6	7	8

Examples:

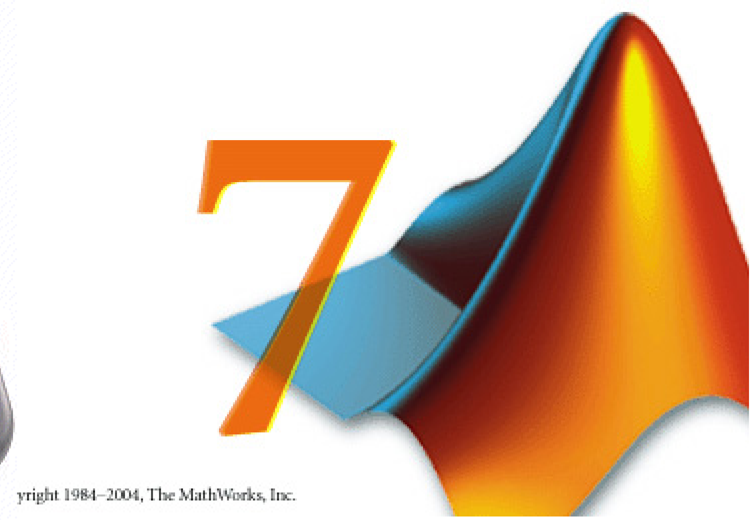
$\lg 3.674 = 0.5647 + 0.0005 = 0.5652$
$\lg 367.4 = \lg(3.674 \times 10^2) = 2.5652$
$\lg 0.003674 = \lg(3.674 \times 10^{-3}) = \bar{3}.5652$

Constant	π	e	lg e	ln10
Value	3.14159	2.71828	0.43429	2.30259
log (base 10)	0.49715	0.43429	$\bar{1}.63778$	0.36222





MATLAB®
The Language of Technical Computing



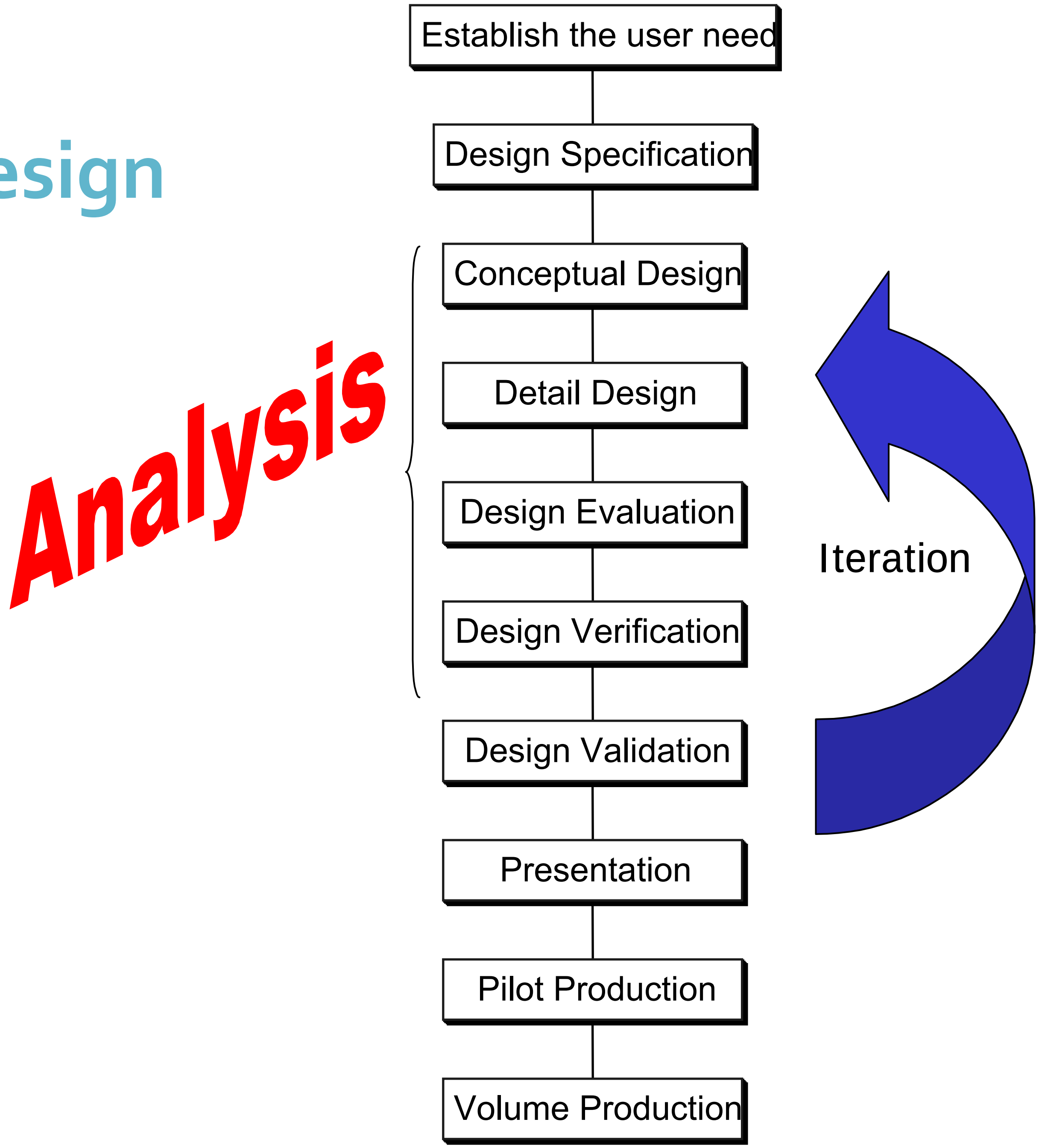
Large scale computational software

- Various physics
  - Solid mechanics
  - Fluid mechanics
  - Heat and mass transfer
  - Electromagnetics
- Such analyses have moved from research to design

Some advantages of Simulation-based design over prototype-based

- Testing “what-if” scenarios can be quick and inexpensive
- Can reduce cost
- Can reduce time to market, help compete by making shorter product cycles
- Dramatic changes are easier to conceive

Phases of Biomedical Design



Conceptual Design Phase: How computing can help

- Generate as many potential alternative solutions to the problem as possible and evaluate them
  - Can be less time and resource consuming to test feasibility
  - Can include truly dramatic ideas
  - Can help in alternative idea generation
  - Can provide more detailed and quantitative information than possible experimentally

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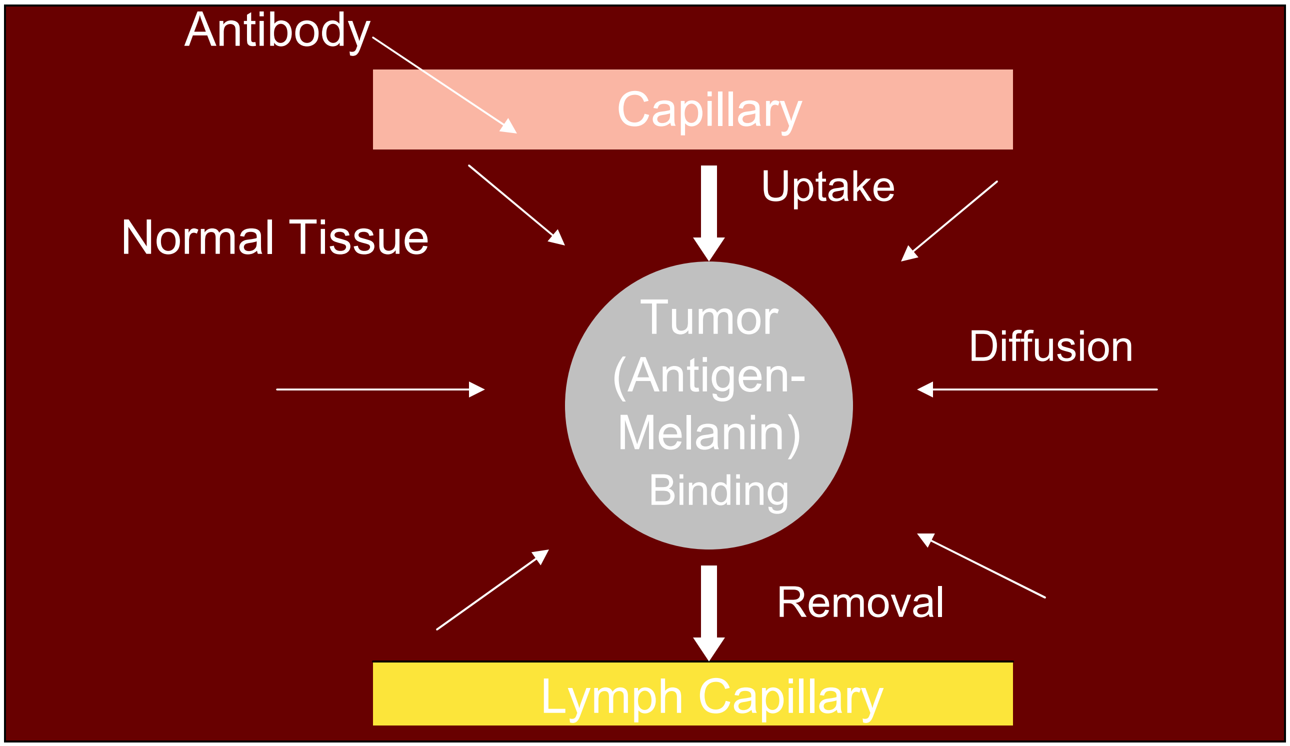
- Challenges in Biological Engineering

Metastatic Melanoma

- **Melanoma**: Malignant tumor in the cells of bottom layer of the skin's epidermis and middle layer of the eye, most dangerous form of skin cancer
- Treatment: Radioimmunotherapy (RIT)
- In RIT, the antibody binds to a tumor-associated antigen to deliver a lethal dose of radiation to tumor cells.

Joint work with Albert Einstein College of Medicine



The need for computational model

- Next step???
- Preparation of clinical trials in human to examine the effect of different parameters
  - Different melanin concentrations (representing different patients)
  - Different diffusivities (representing different antibody or tissue type)
- Computational model for RIT

Mathematical Description

- Antibody uptake from blood:

$$c_{Abp}\left(t\right) = c_{Ab0}e^{-\lambda t}$$

- Transport, uptake and clearance of antibody in normal tissue

$$\frac{\partial c_{Abt}}{\partial t} = D_{tis}\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_{Abt}}{\partial r}\right) + k^{bl}c_{Abp} - k^{ly}c_{Abt}$$

- Transport, complex formation and dissociation in tumor

$$\frac{\partial c_{Ab}}{\partial t} = D_{tum}\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_{Ab}}{\partial r}\right) - k_{+1}c_{Ab}c_{Ag} + k_{-1}c_{Ab-Ag}$$

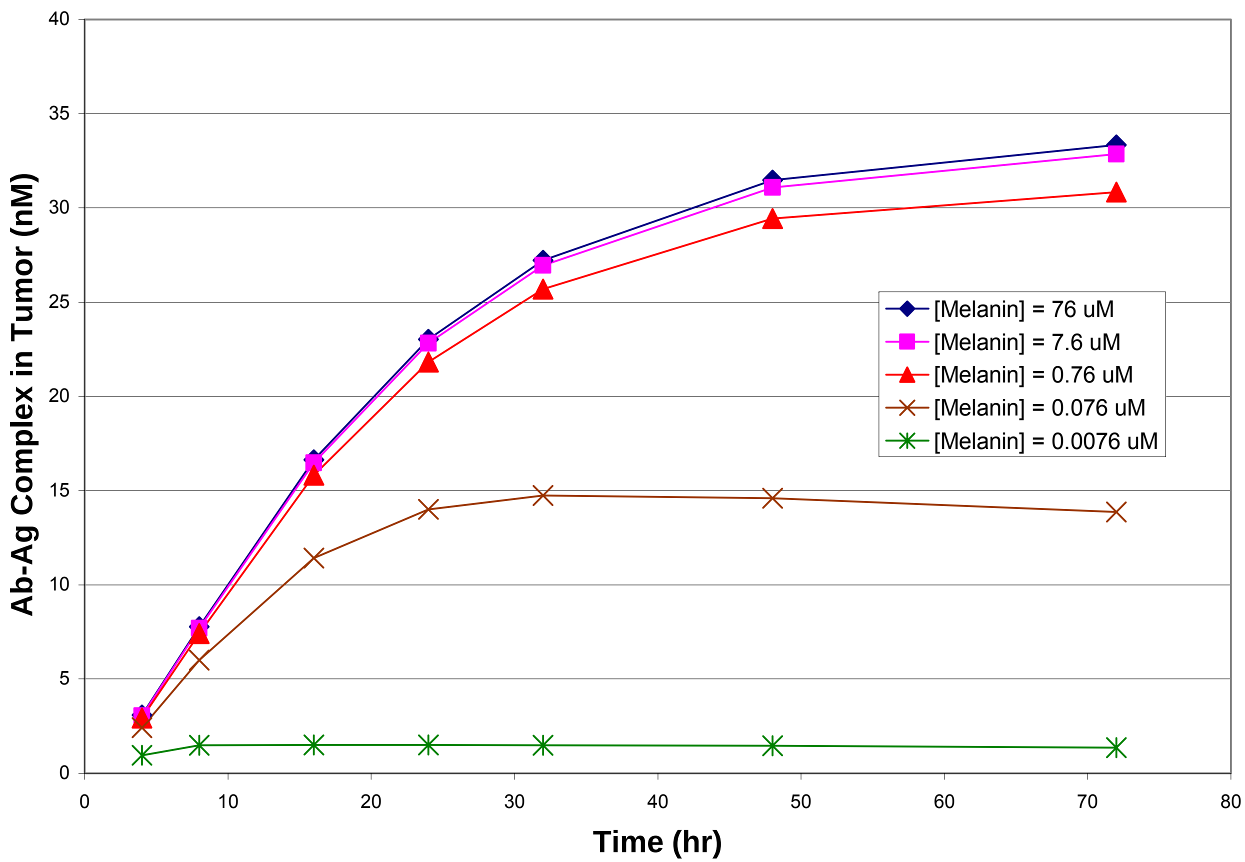
- Antigen concentration due to complex formation and dissociation

$$\frac{\partial c_{Ag}}{\partial t} = n\left(-k_{+1}c_{Ab}c_{Ag} + k_{-1}c_{Ab-Ag}\right)$$

- Complex concentration due to formation and dissociation

$$\frac{\partial c_{Ab-Ag}}{\partial t} = k_{+1}c_{Ab}c_{Ag} - k_{-1}c_{Ab-Ag}$$

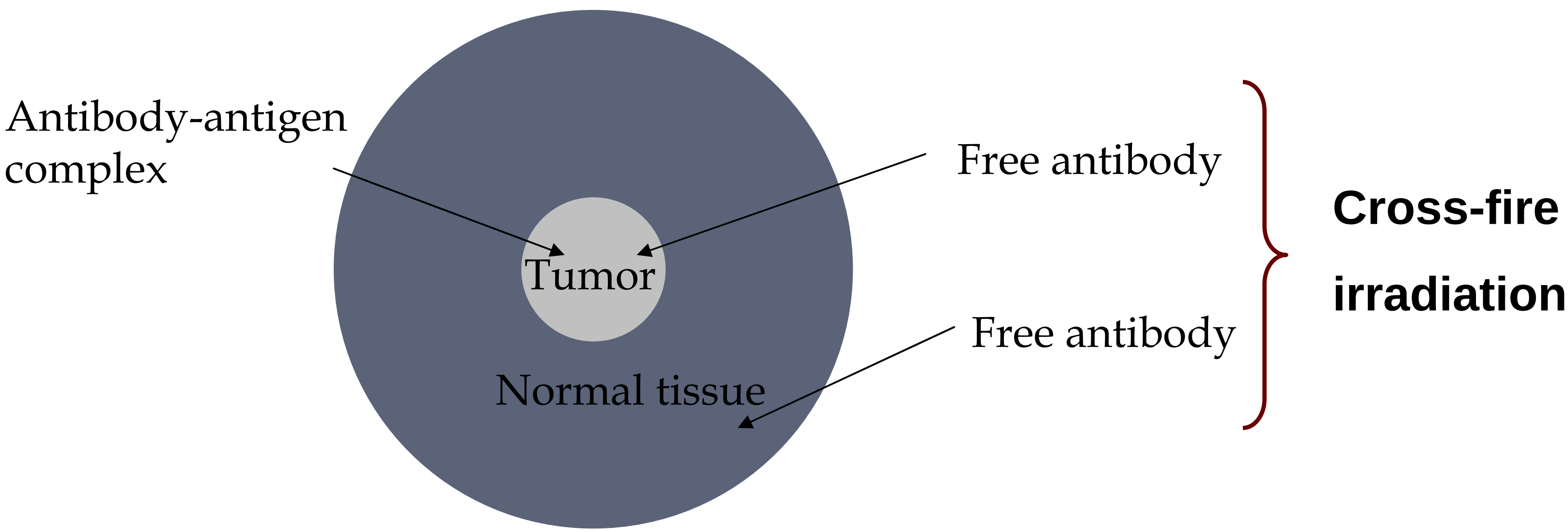
Complex Formation



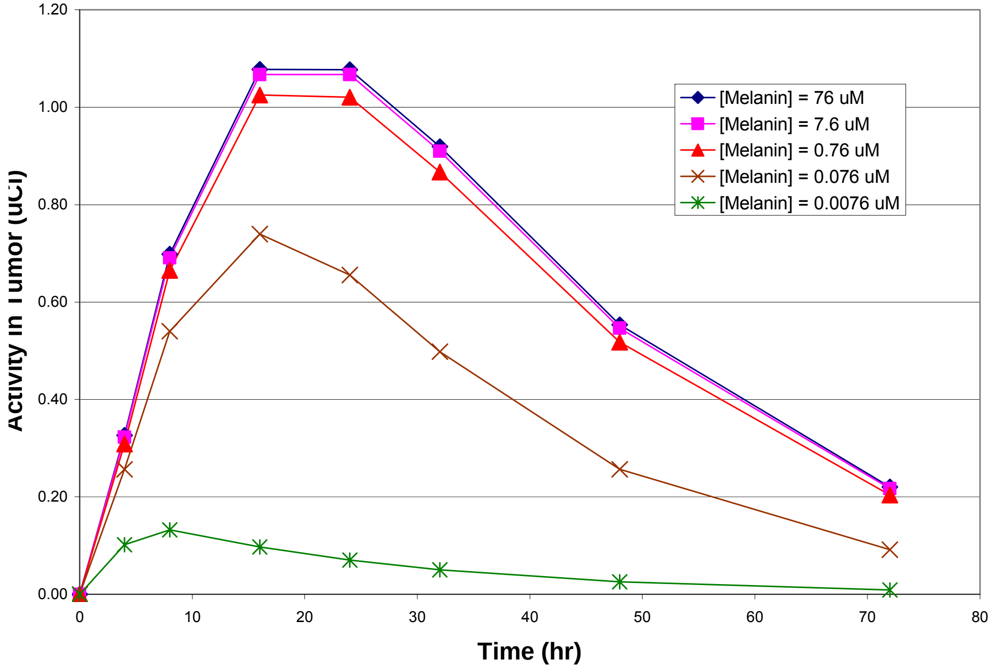
Despite increased penetration at lower melanin concentrations, the average complex concentration in the tumor was remarkably similar for 76, 7.6, and 0.76 μM.

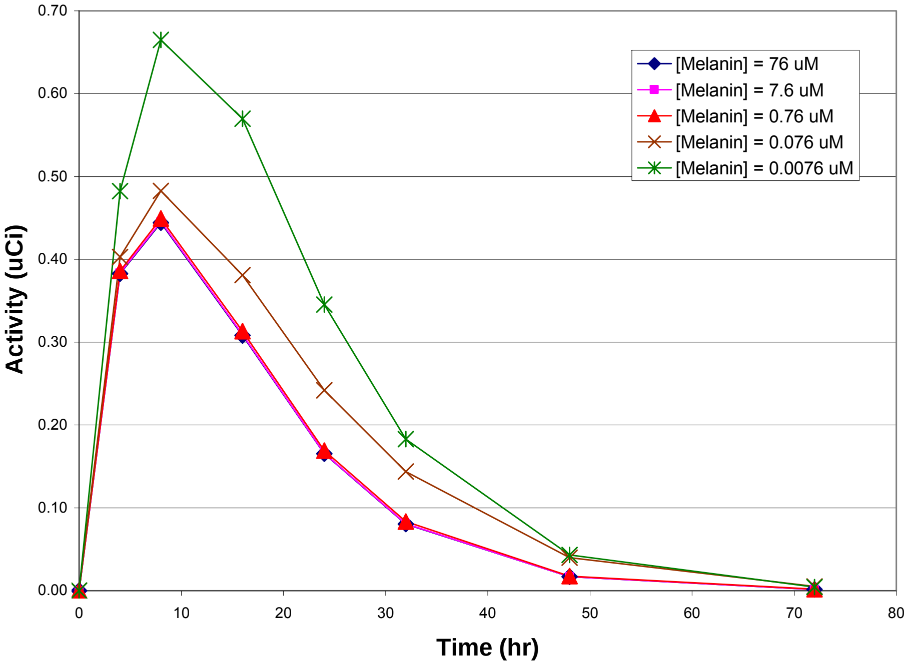
Absorbed Dose Calculation

- Two contributions to lethal dose:
  - Complex in tumor
  - Cross-fire irradiation from free antibody in normal tissue and tumor



Contribution of cross-fire to activity could be easily seen using a model





Activity due to: (a) Complex formation (b) Cross-fire Radiation

Alternative to the computational model

- Experimentation in animals (mice)
- Actual clinical trials in patients
- Difficulties in experimentation:
  - Computational model used to evaluate the effectiveness of the procedure in dissimilar cases of the disease
  - Computational model provides means to investigate antibody types that can be designed in the future- not possible through experiments

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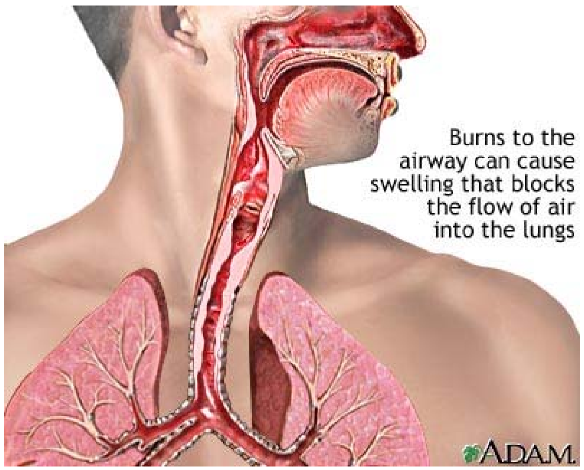
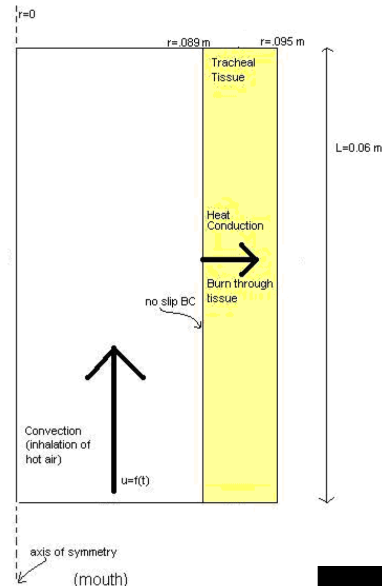
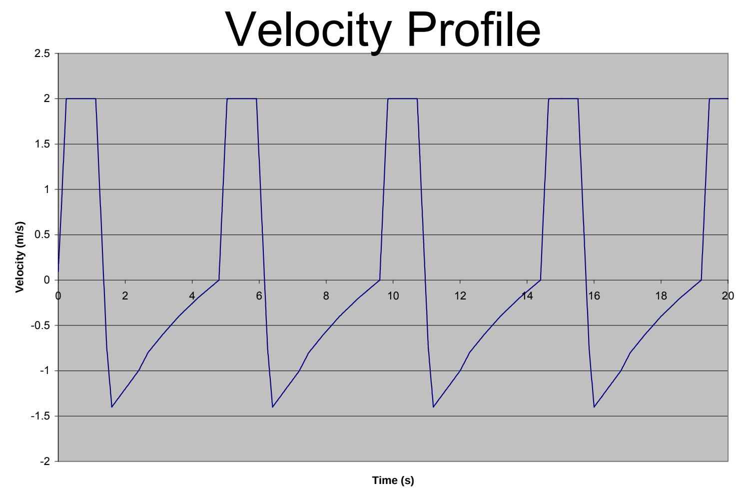
A course on modeling in the context of design

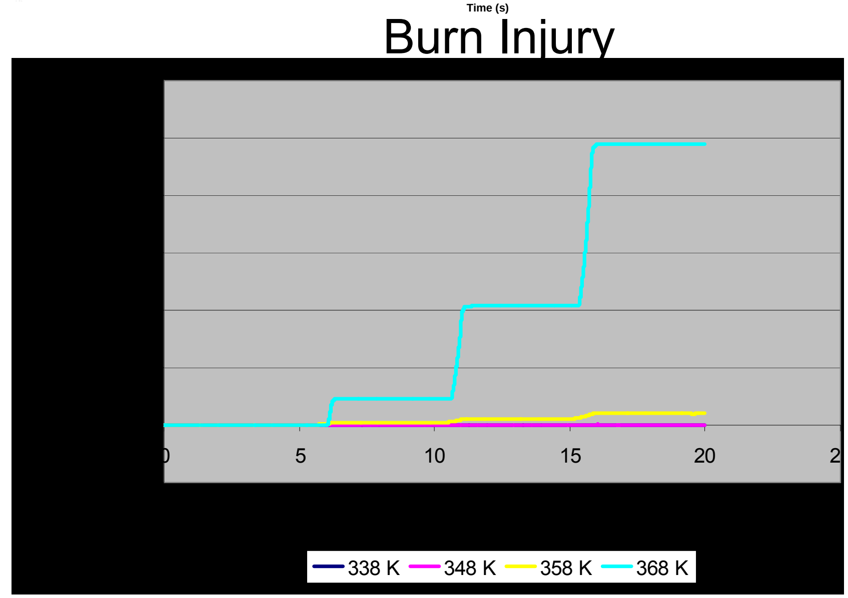
- Engineering Undergraduate Senior and Juniors (40-45 students; 10-11 projects)
- Course content
  - Very short introduction to generic design
  - 8 weeks on
    - Generic aspects (G.E., B.C., Properties,..)
    - Case studies of biomedical processes
  - 2 weeks on software and related instruction
  - Semester long project
  - Oral presentation and report

Example course project: Tracheal burning from hot air inhalation









- Governing Equations:

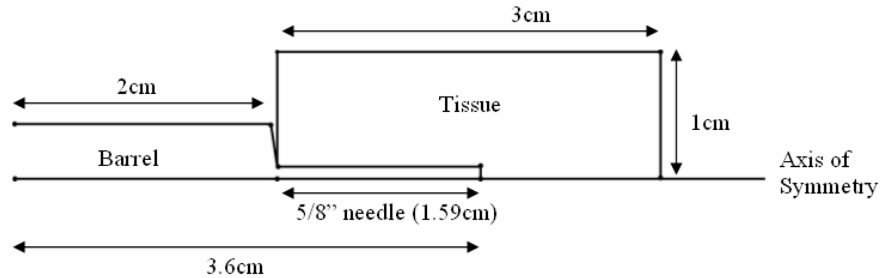
$$\frac{1}{\alpha}\frac{\partial T}{\partial t}=\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}+\frac{W_b C_b}{k}(T_a-T)+\frac{Q}{k}$$

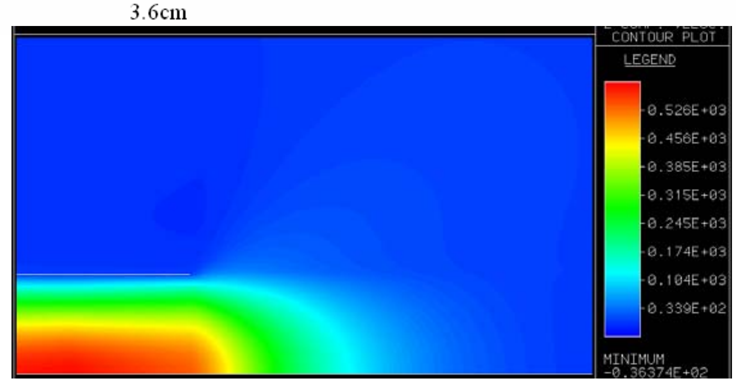
$$\Omega=\int P\exp\left(\frac{\Delta E}{RT}\right)dt$$

$$\rho\left(\frac{\partial u}{\partial t}+u\cdot\nabla u\right)=-\nabla p+\mu\nabla^2 u$$

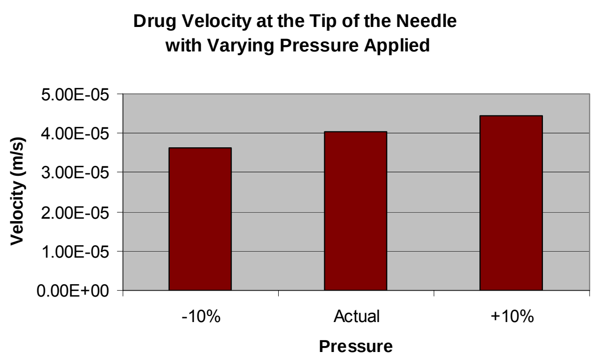
Example course project: Design of Auto-Syringe Injection

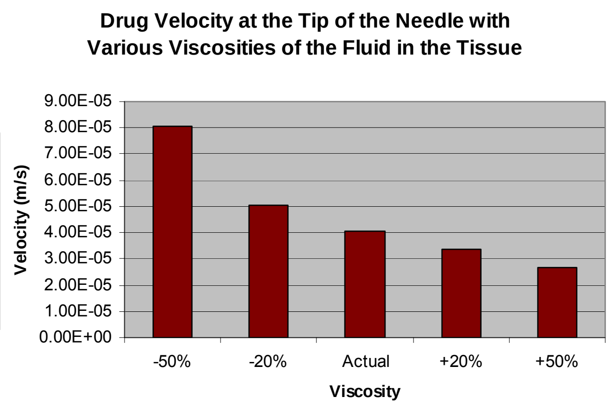
- Auto-Syringe: An automatic device that allows patients with limited dexterity to administer medication to themselves
- Design Requirements:
  - 3 seconds injection
  - 10 pounds of force on plunger
  - Compatible with current pre-filled syringes





Velocity Contour Plot



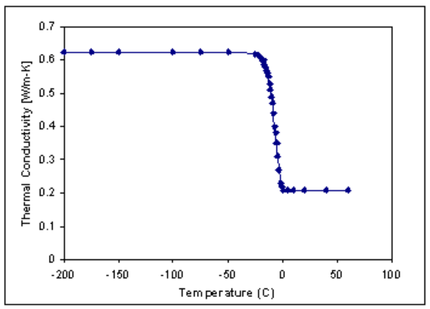


Challenges for a novice audience

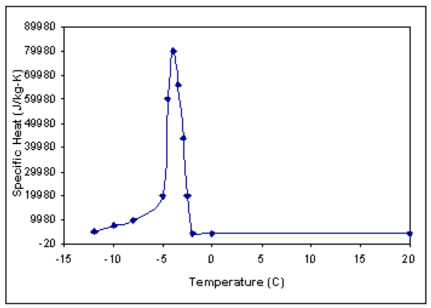
- How to skim through a lot of computing concepts
  - Develop specialized coursenotes
- How to give enough training in a complex software in a very short time?
  - Develop tutorials
- How to provide guidance to 10-11 independent projects
  - Develop generic guidance to model building
  - Need TA/Support person with background and interest
  - Develop resource database

Example Tutorial: Cryosurgery

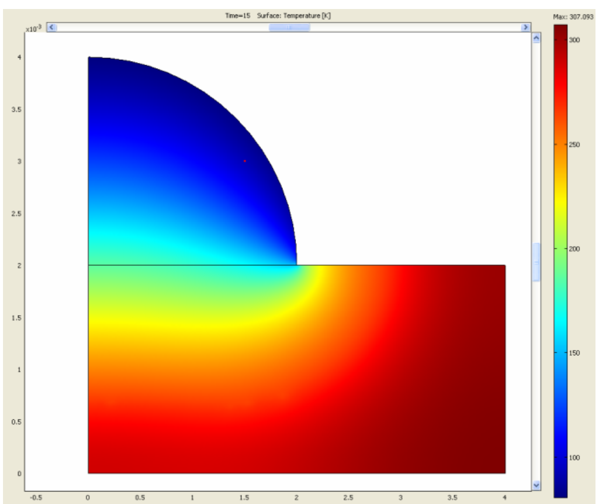
Thermal Conductivity



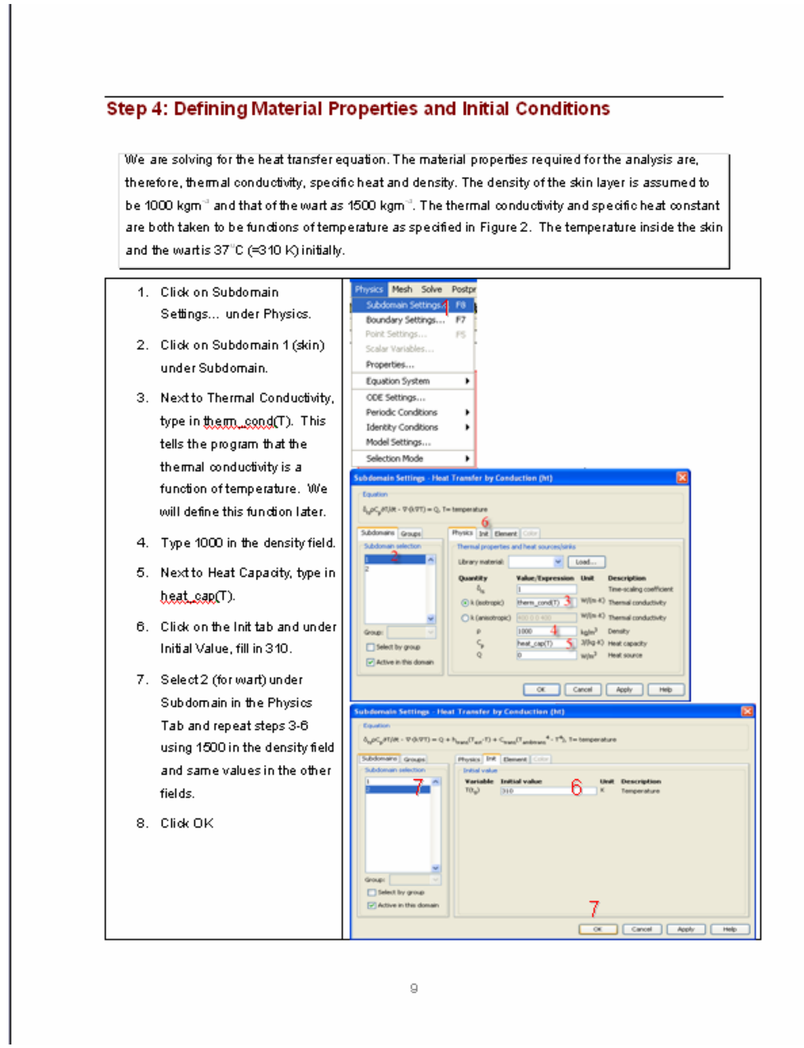
Specific heat



Temperature contours



Sample window:



Step 4: Defining Material Properties and Initial Conditions

We are solving for the heat transfer equation. The material properties required for the analysis are, therefore, thermal conductivity, specific heat and density. The density of the skin layer is assumed to be 1000 kgm⁻³ and that of the wart as 1500 kgm⁻³. The thermal conductivity and specific heat constant are both taken to be functions of temperature as specified in Figure 2. The temperature inside the skin and the wart is 37°C (=310 K) initially.

1. Click on Subdomain Settings... under Physics.
2. Click on Subdomain 1 (skin) under Subdomain.
3. Next to Thermal Conductivity, type in therm_cond(T). This tells the program that the thermal conductivity is a function of temperature. We will define this function later.
4. Type 1000 in the density field.
5. Next to Heat Capacity, type in heat_cap(T).
6. Click on the Init tab and under Initial Value, fill in 310.
7. Select 2 (for wart) under Subdomain in the Physics Tab and repeat steps 3-6 using 1500 in the density field and same values in the other fields.
8. Click OK

9

Course introduces several design aspects

- Intro to generic design issues
- Open-ended
- Interdisciplinary
- Culminating
- Group work
- “what-if” scenarios
- Variability
- Optimization
- Closer to real world
- Presentation (oral and written)

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State of adoption in industry is low but increasing significantly

- State of adoption is low compared to automotive, aeronautics, etc.
- In the last few years, activities have increased considerably
- Many software companies are pushing bio applications as their growth area
- Software that can do multiphysics are being particularly effective
- Acquisition of real geometry is helping in the process

Example of current activities

- Workshop on Computer Methods for Cardiovascular Device Design and Evaluation on March 18, 19
  - FDA
  - NIH Heart, Lung and Blood Institute
  - NSF

Challenges in including computing to biological engineering design

- Processes can be more complex and multidisciplinary
- Materials can change more significantly
- Needs more resource development
  - Computing resource (properties database; understanding,..)
  - Human resource
- Culture not as friendly to computing
- Bio-friendly software interfaces can make it even easier to integrate computing

Acknowledgement

- Teaching Assistants and Students of BEE 453 at Cornell University for the last 13 years
- Andrew Schweitzer and other co-authors of melanoma research from the AECOM

Thank You