Formulation of Protein Based Drugs

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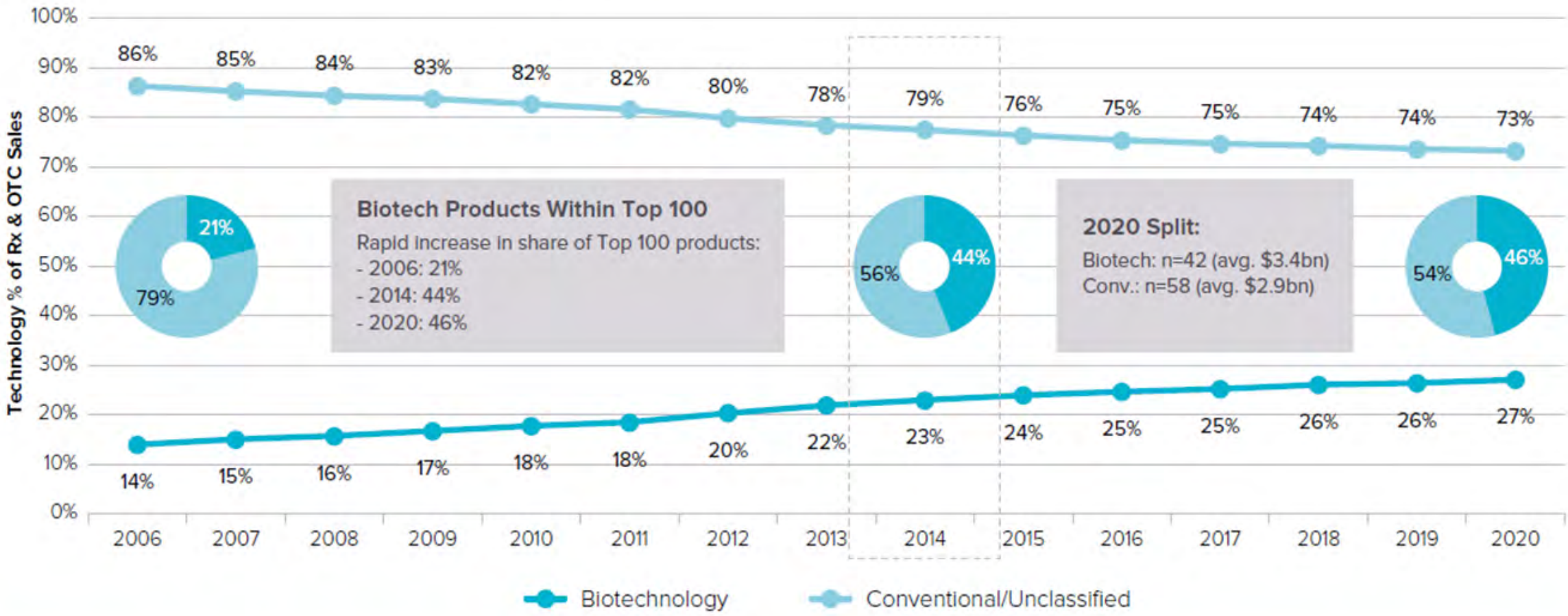
Vice-President Communications, EIPG

The emergence of biologicals

Worldwide Prescription Drug & OTC Pharmaceutical Sales: Biotech vs. Conventional Technology (2006-2020)

Source: EvaluatePharma® 22 May 2015



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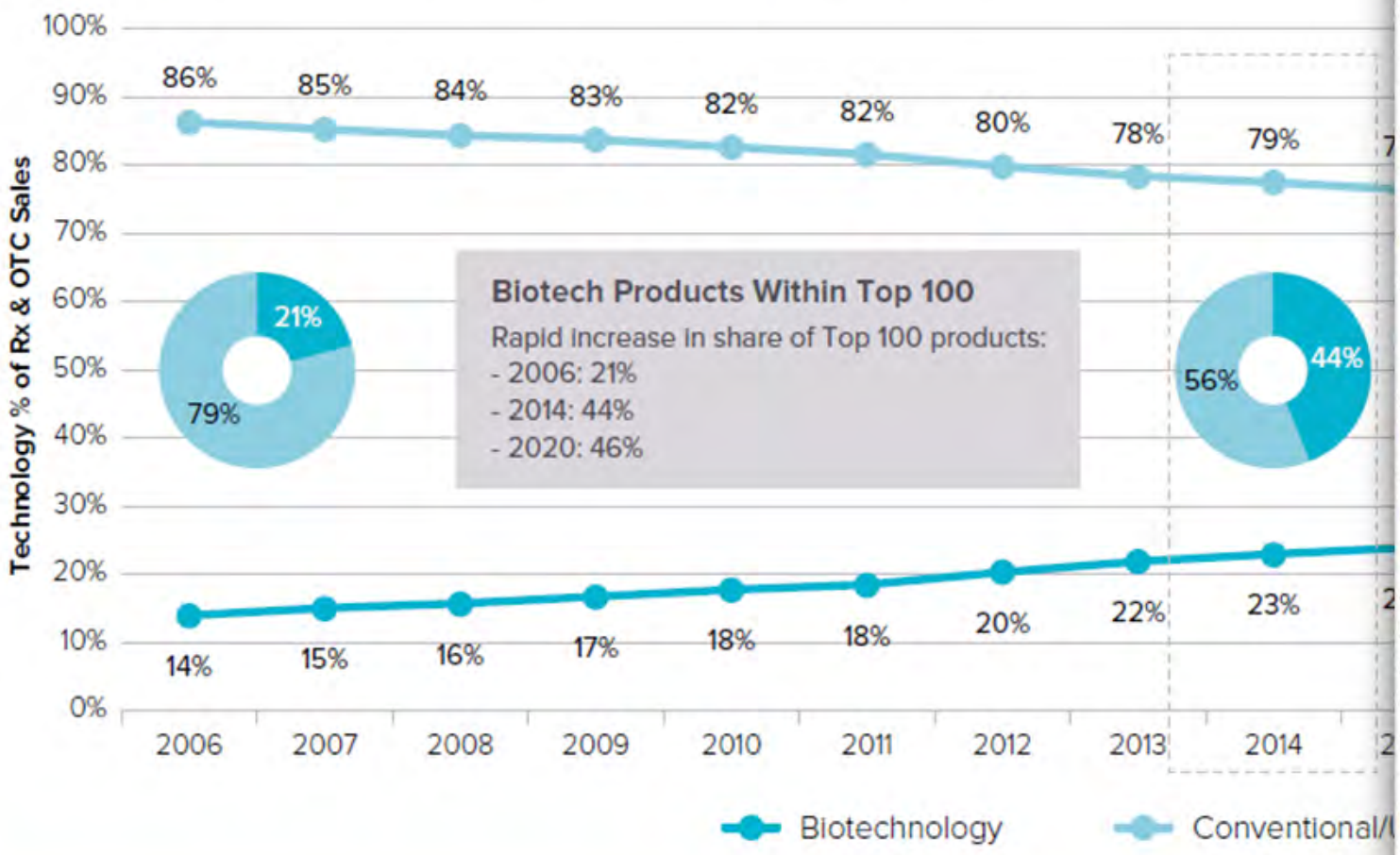
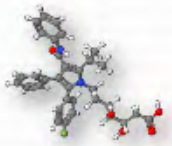


Biggest selling drugs of all time

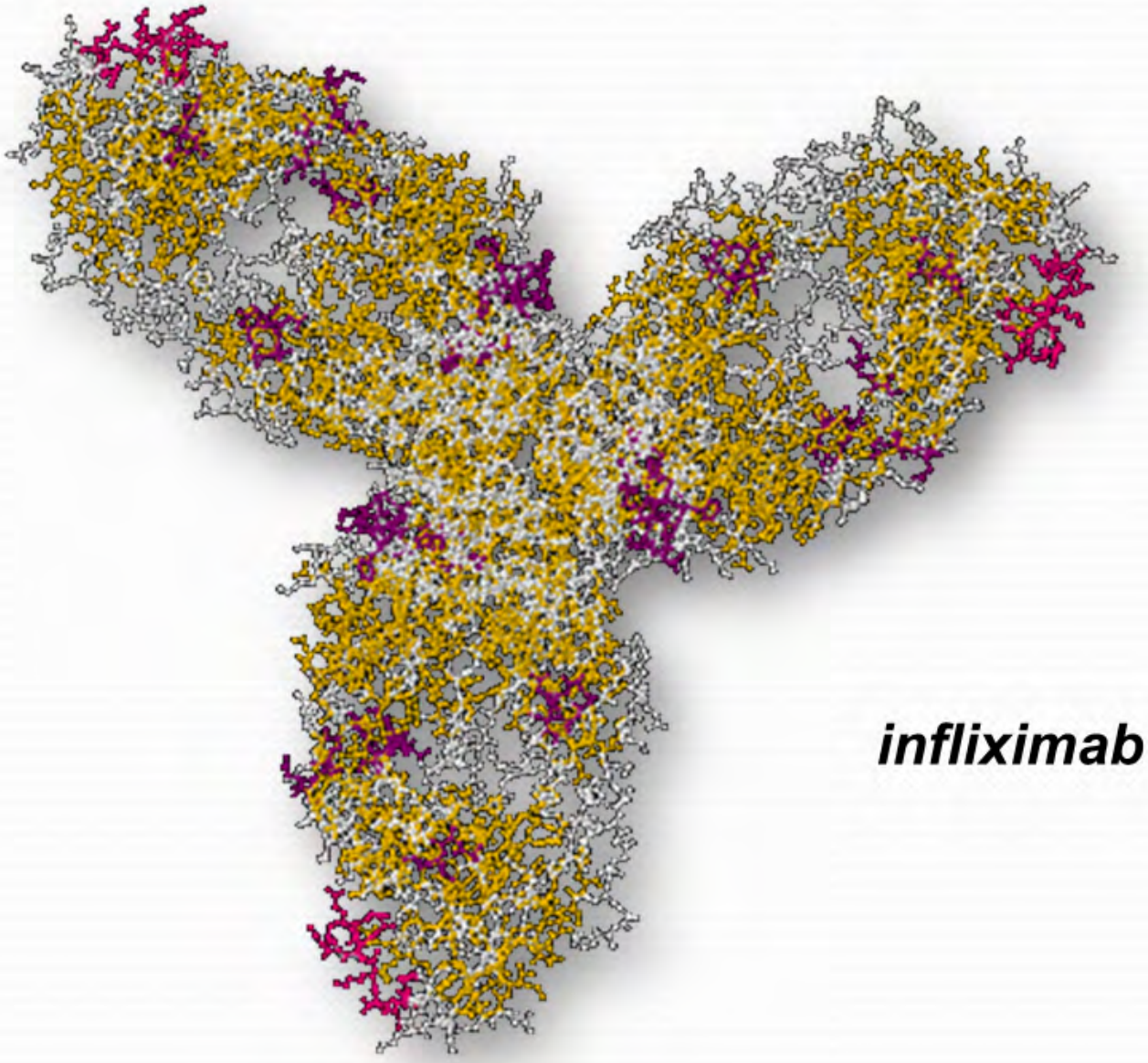
Product	Generic name	Peak year sales	$m	Type
Lipitor	atorvastatin	2006	13696	Small molecule
Humira	adalimumab	2014	12543	Biologic
Sovaldi/ Harvoni	sofosbuvir/ ledipasvir	2014	12410	Small molecule
Plavix	clopidogrel	2011	9927	Small molecule
Abilify	aripiprazole	2013	9502	Small molecule
Remicade	infliximab	2014	9240	Biologic
Enbrel	etanercept	2014	8538	Biologic
Lantus	insulin glargine	2014	8433	Biologic
Seretide	fluticasone/ salmeterol	2013	8235	Small molecule
Rituxan	rituximab	2014	7550	Biologic
Avastin	bevacizumab	2014	7021	Biologic
Herceptin	trastuzumab	2014	6866	Biologic
Crestor	rosuvastatin	2011	6622	Small molecule
Losec	omeprazole	2000	6260	Small molecule
Diovan	valsartan	2010	6053	Small molecule
Januvia/ Janumet	sitagliptin	2014	6002	Small molecule
Seroquel	quetiapine	2011	5828	Small molecule
Singulair	motelukast	2011	5479	Small molecule
Zocor	simvastatin	2002	5216	Small molecule
Nexium	esomeprazole	2007	5216	Small molecule
Lyrica	pregabalin	2014	5168	Small molecule
Zyprexa	olanzapine	2010	5026	Small molecule

Source: Company reported data

Biologicals: not a small molecule



atorvastatin

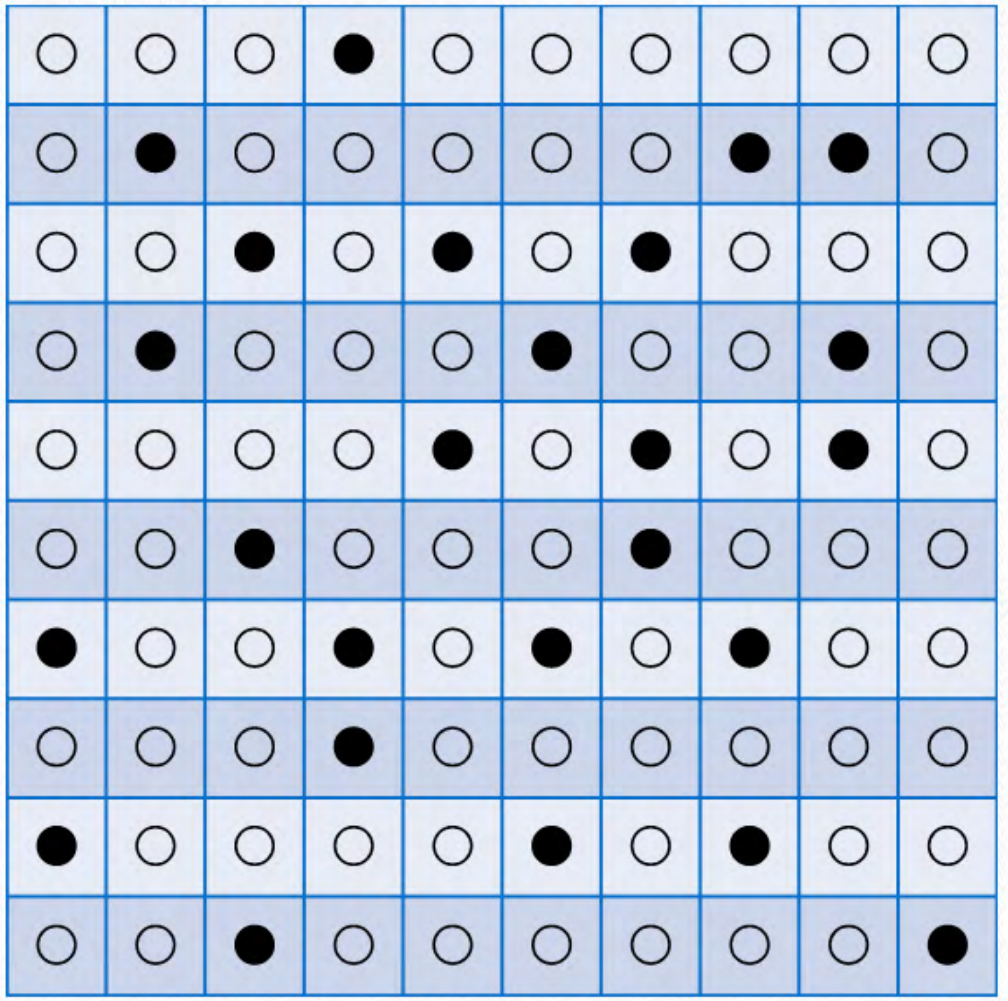


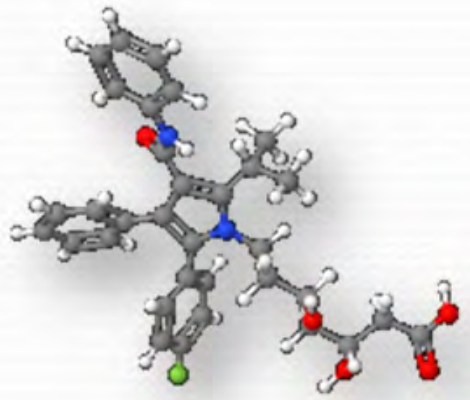
infliximab

Formulation of protein-based drugs

The Solubility Challenge

The Flory-Huggins solution theory





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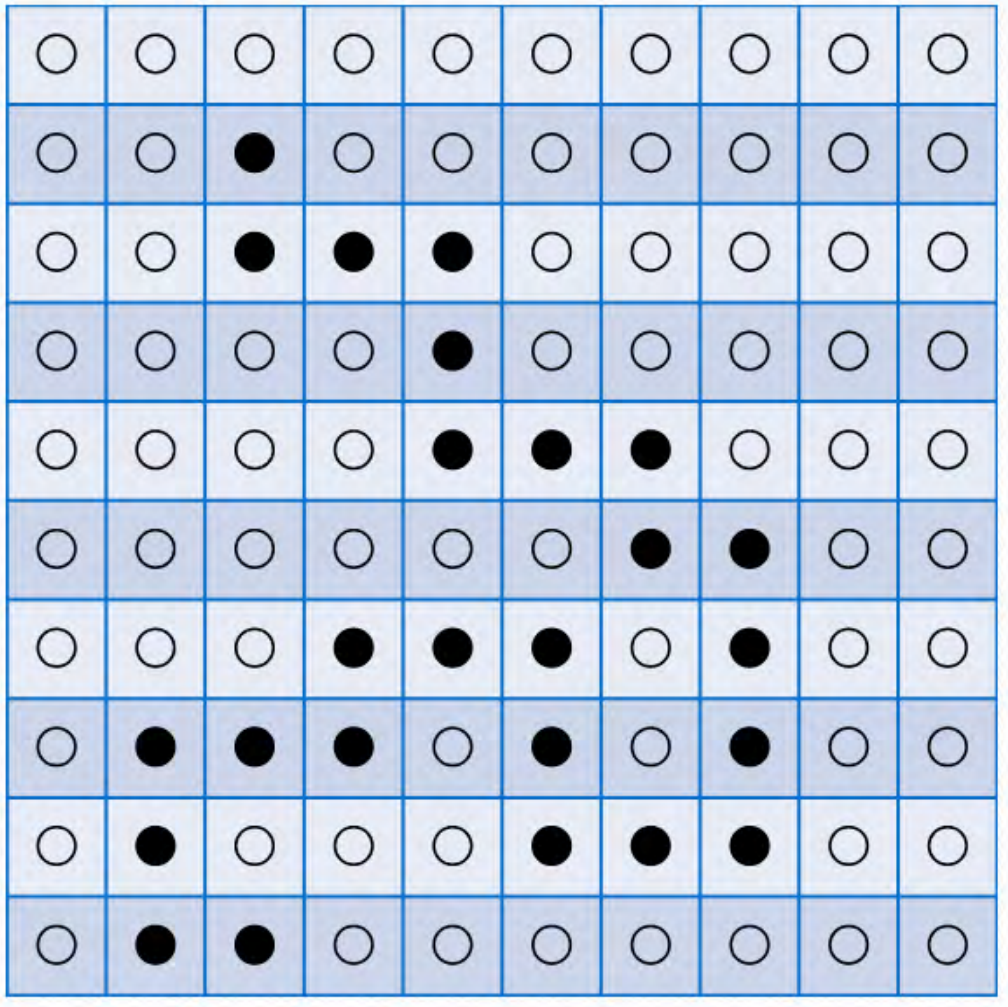

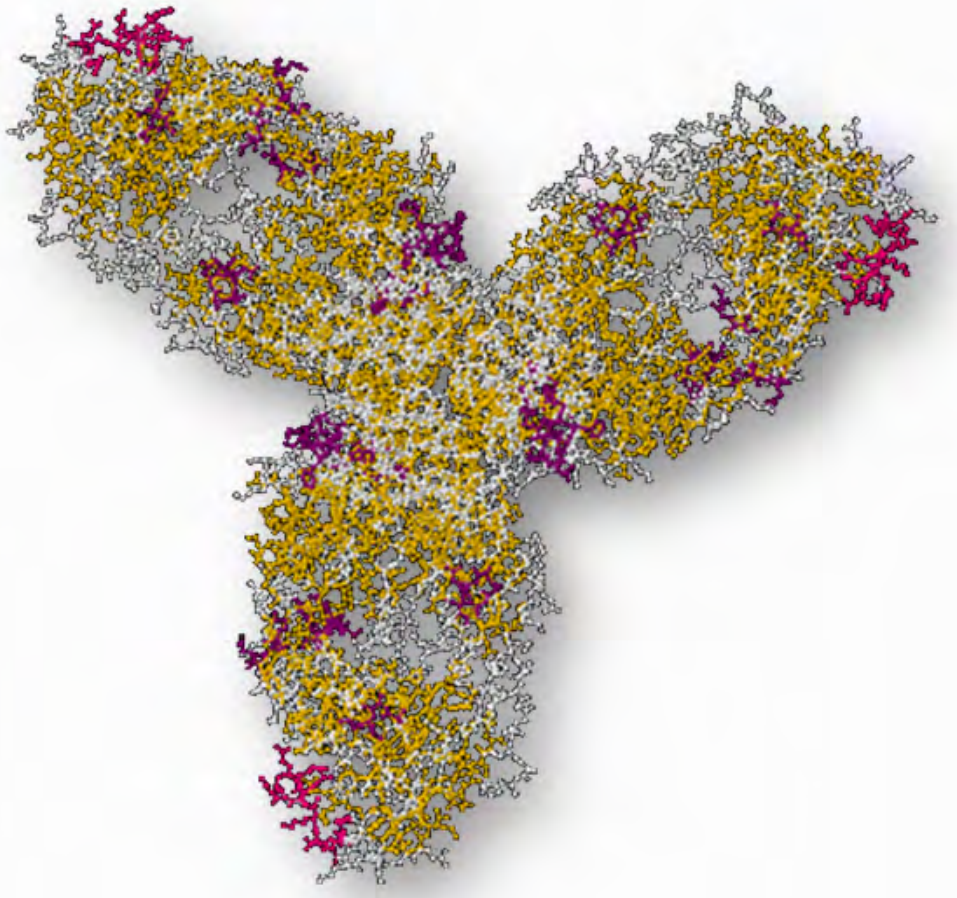

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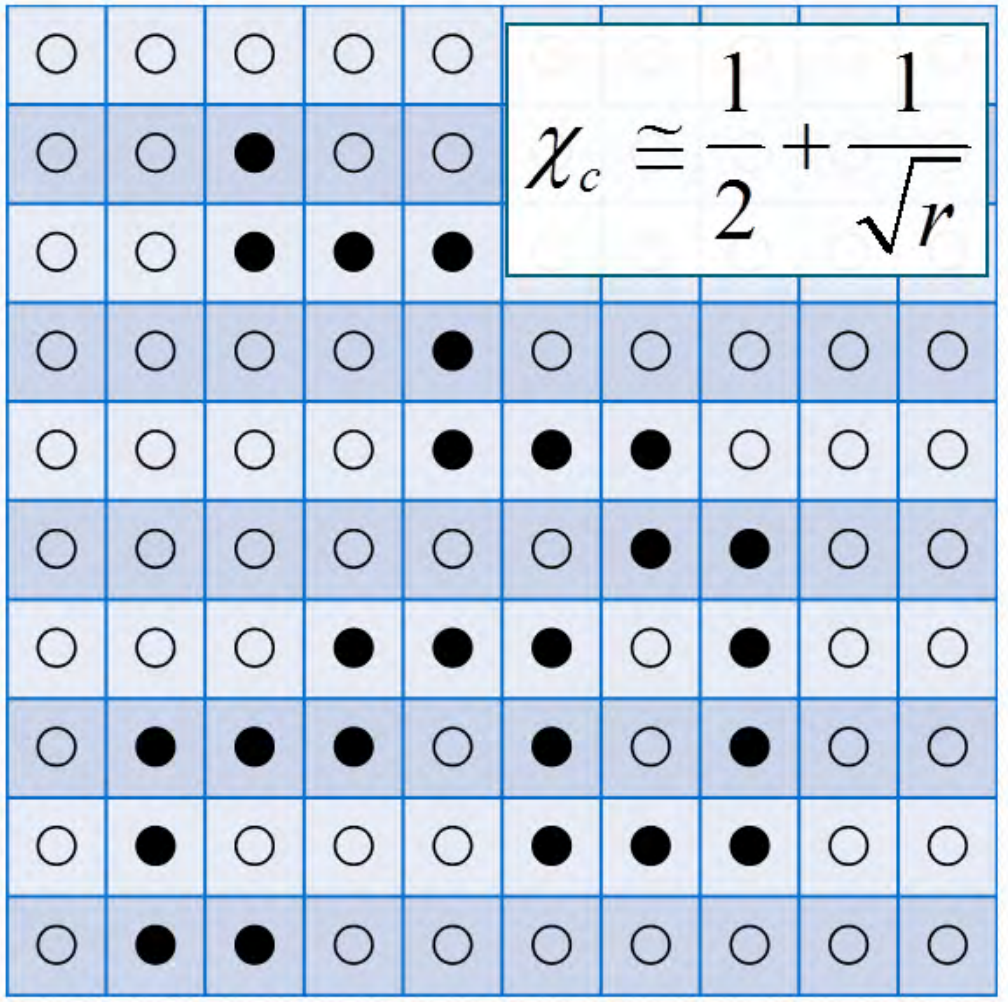
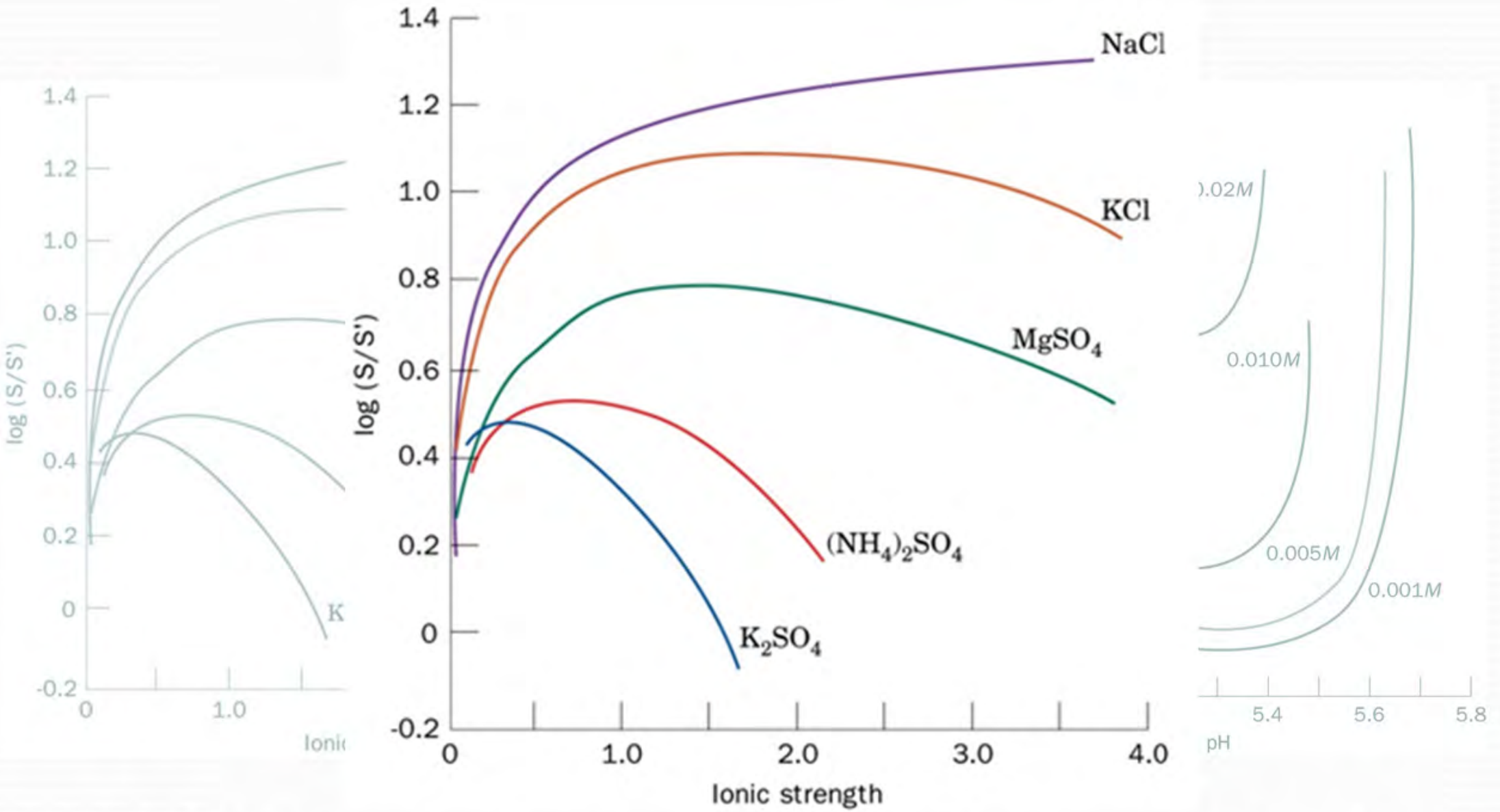


$$\chi_c \cong \frac{1}{2} + \frac{1}{\sqrt{r}}$$

Entropy of mixing a low-molecular-weight solvent with a high-molecular-weight polymer is smaller than that for a low-molecular-weight solute.

Increasing r (the number of polymer chain segments) decrease the critical value of χ_c, the solvent-polymer interaction parameter, and hence decreases solvency of the molecule.

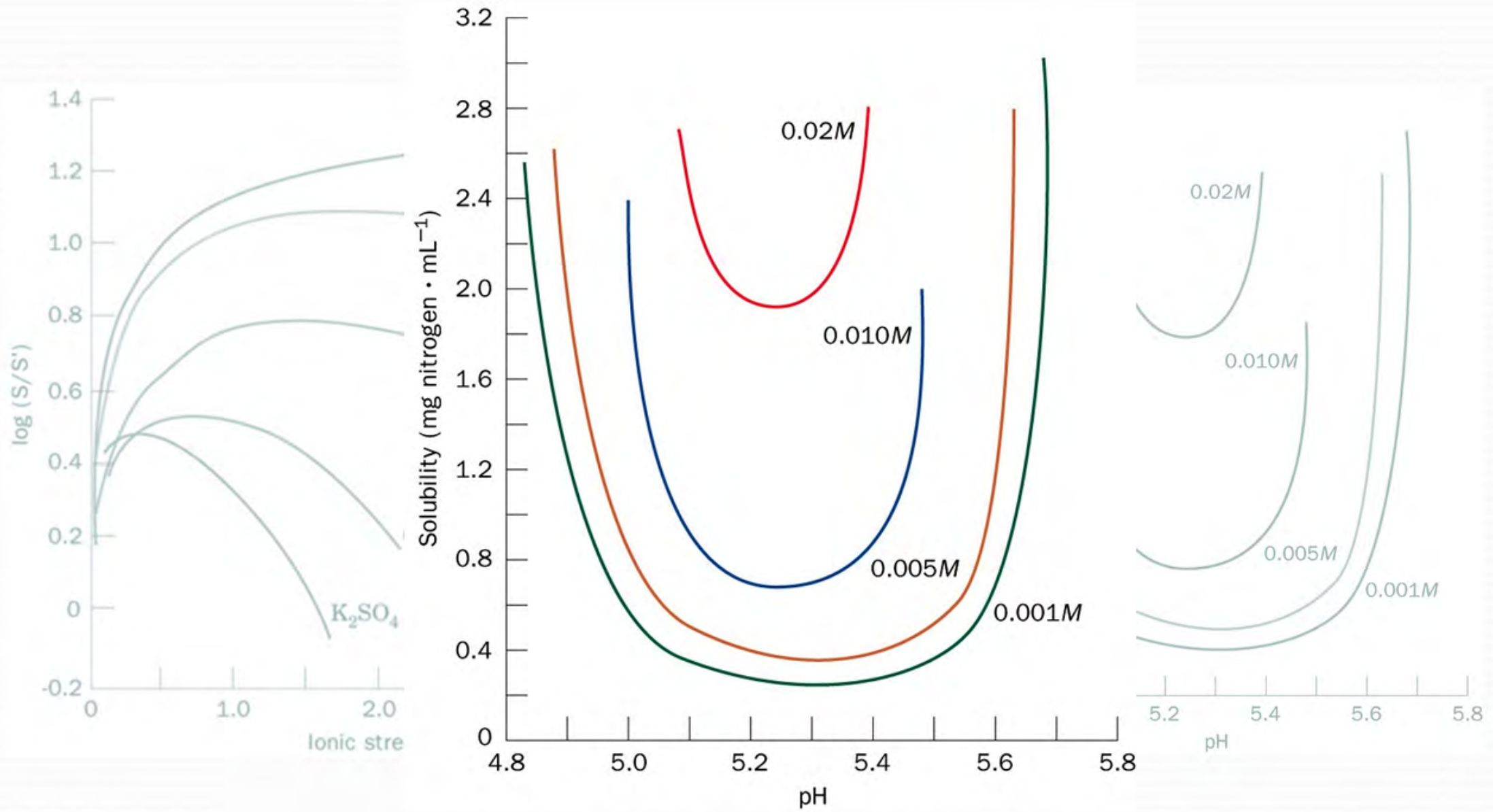
The Hofmeister lyotropic series



Solubility of carboxyhemoglobin at its isoelectric point

Voet and Voet, 2004

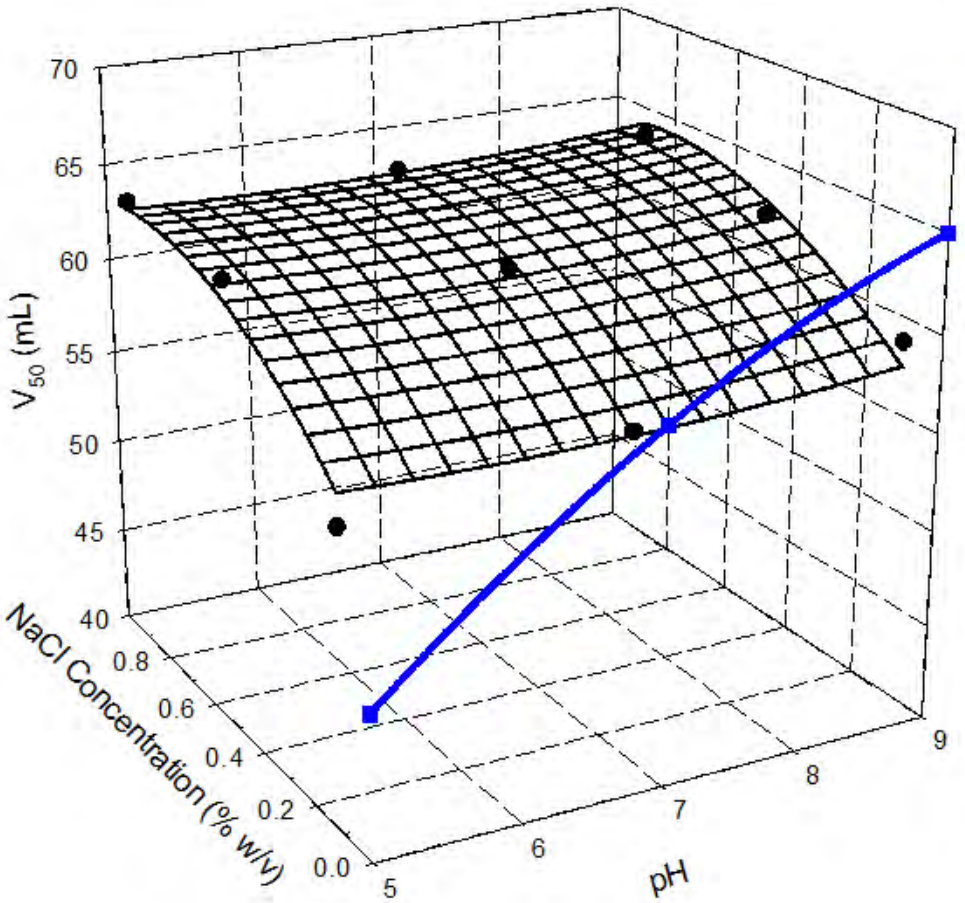
The Hofmeister lyotropic series



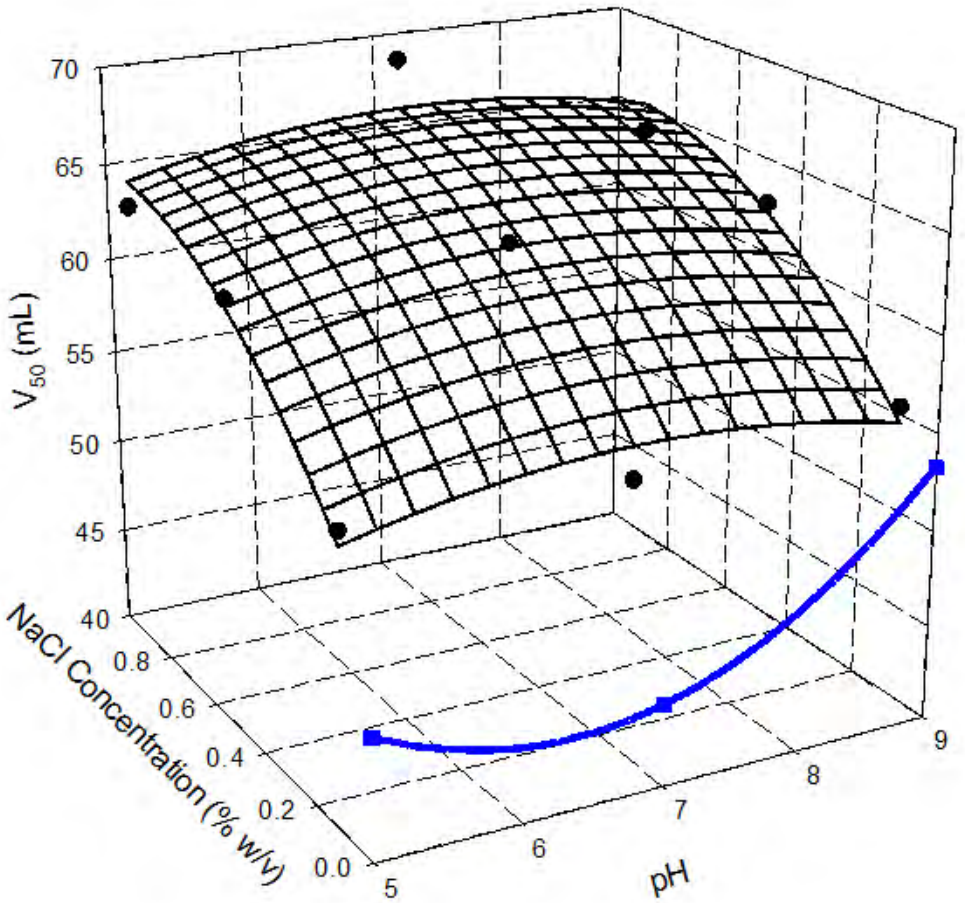
Solubility of β-lactoglobulin

Voet and Voet, 2004

Solubility: a physicochemical challenge



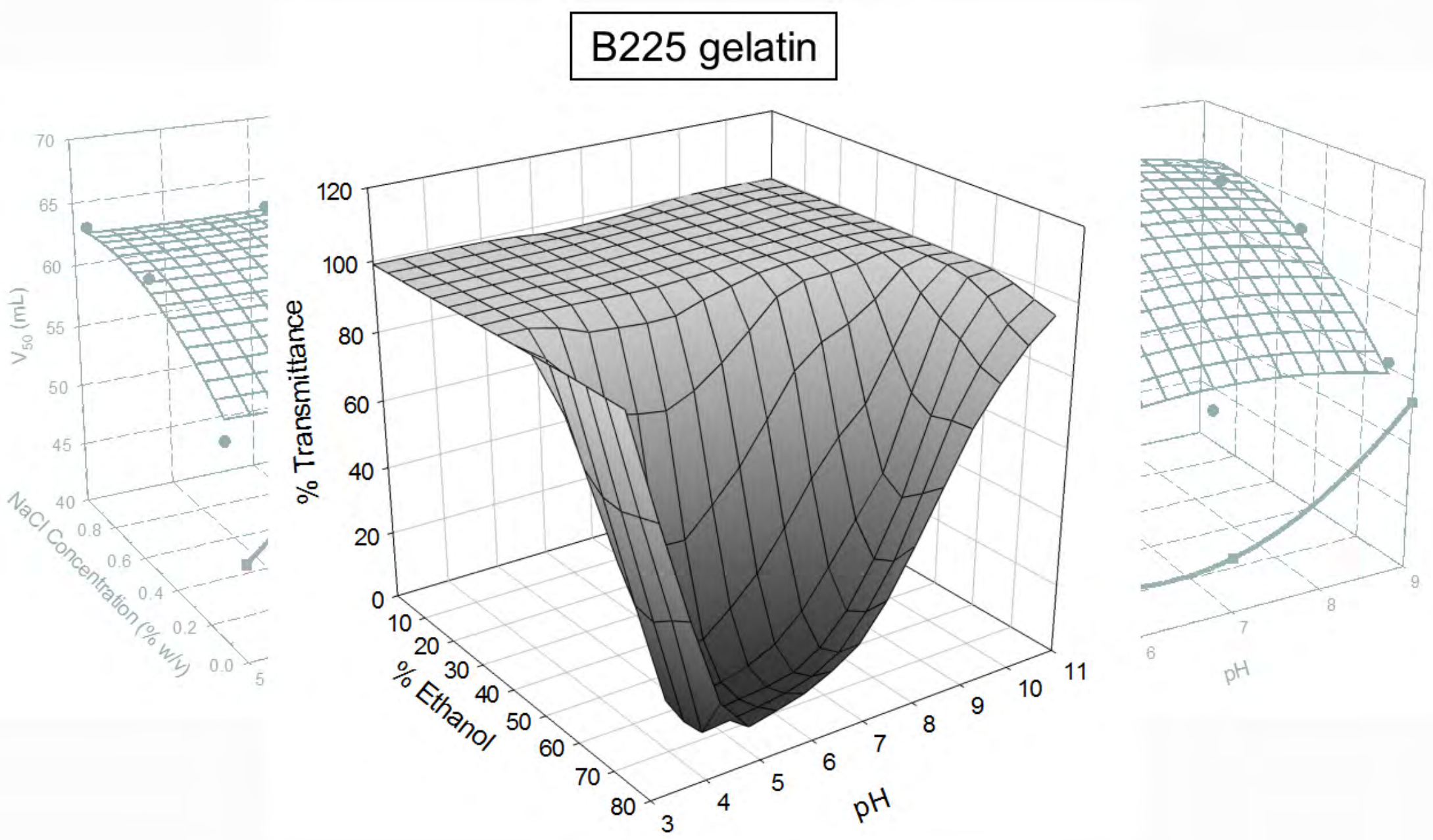
B75 gelatin



A175 gelatin

Aquilina et al., Nuremberg, 2004

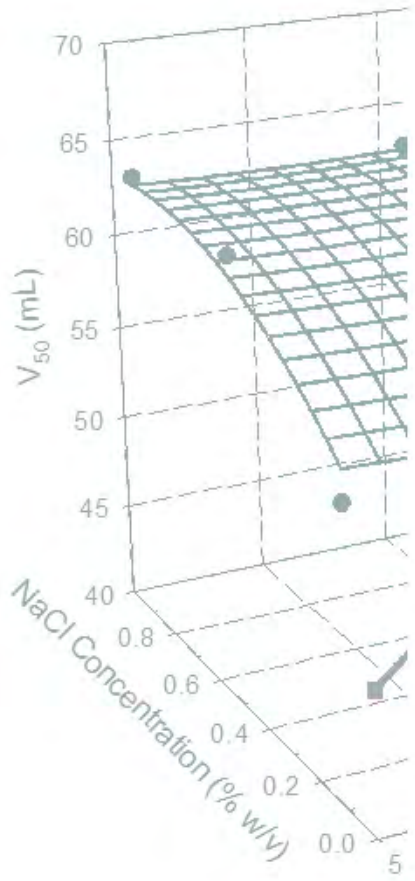
Solubility: a physicochemical challenge

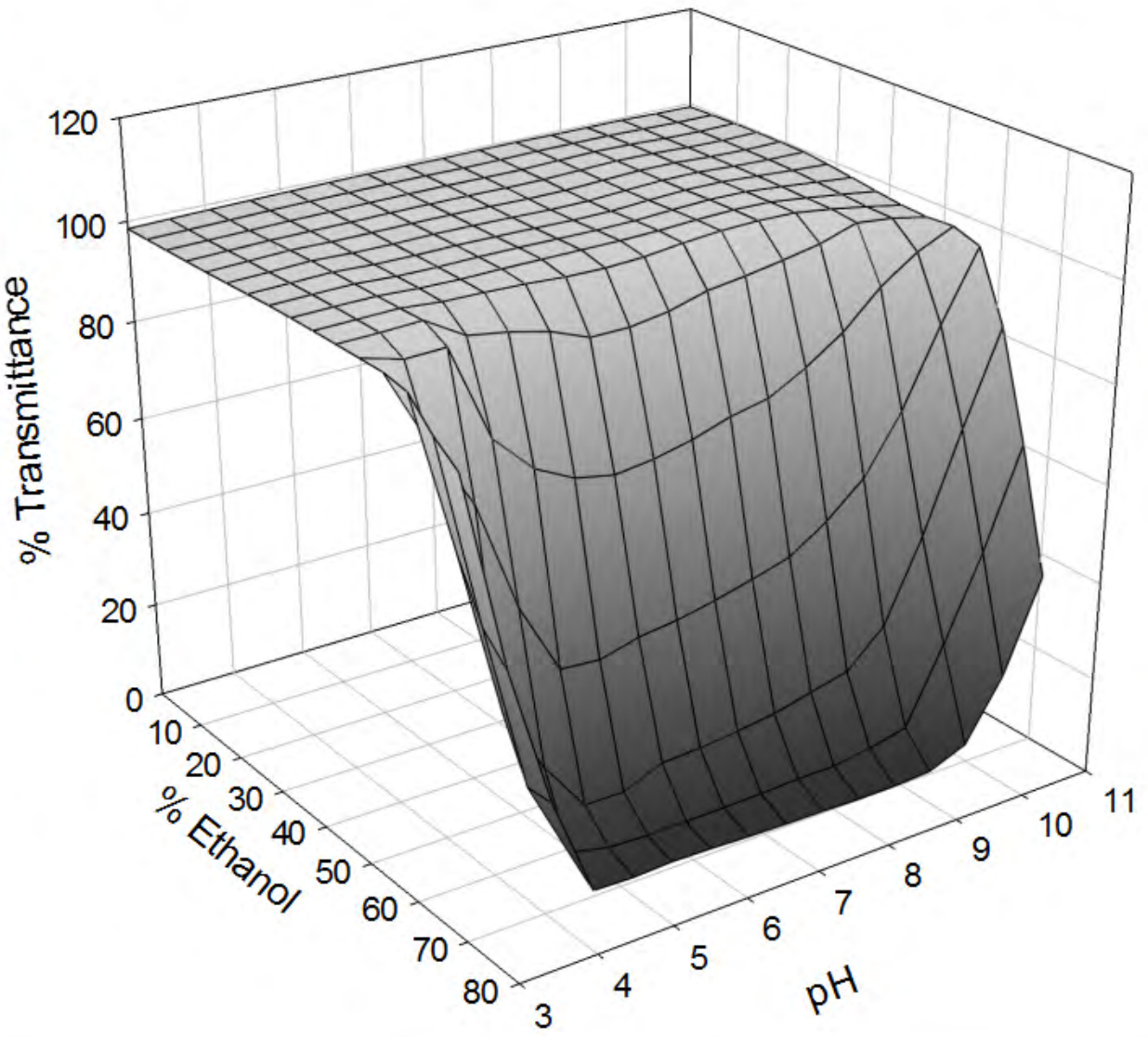


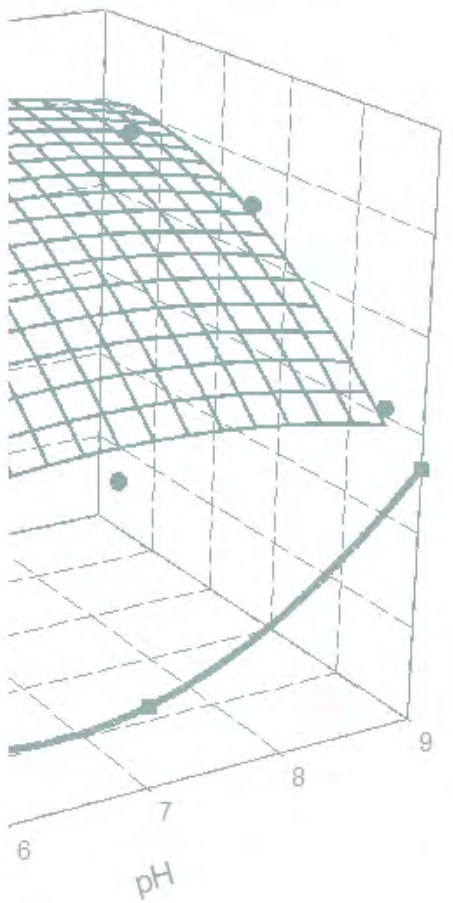
Storm et al., Geneva, 2006

Solubility: a physicochemical challenge

B225 gelatin with 0.1% w/v NaCl



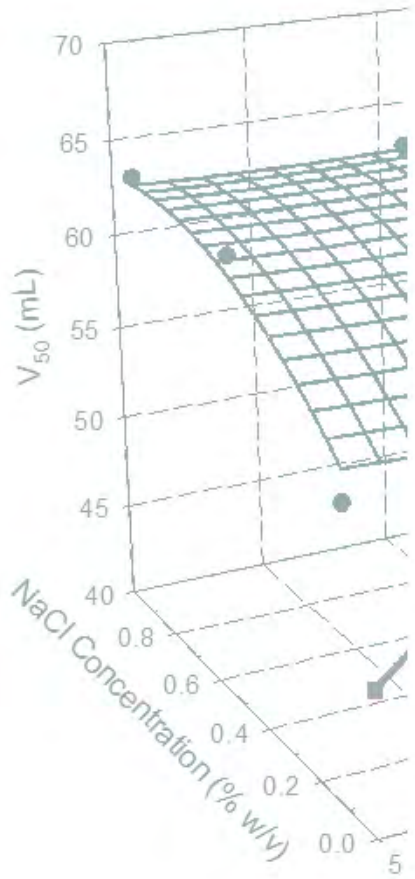


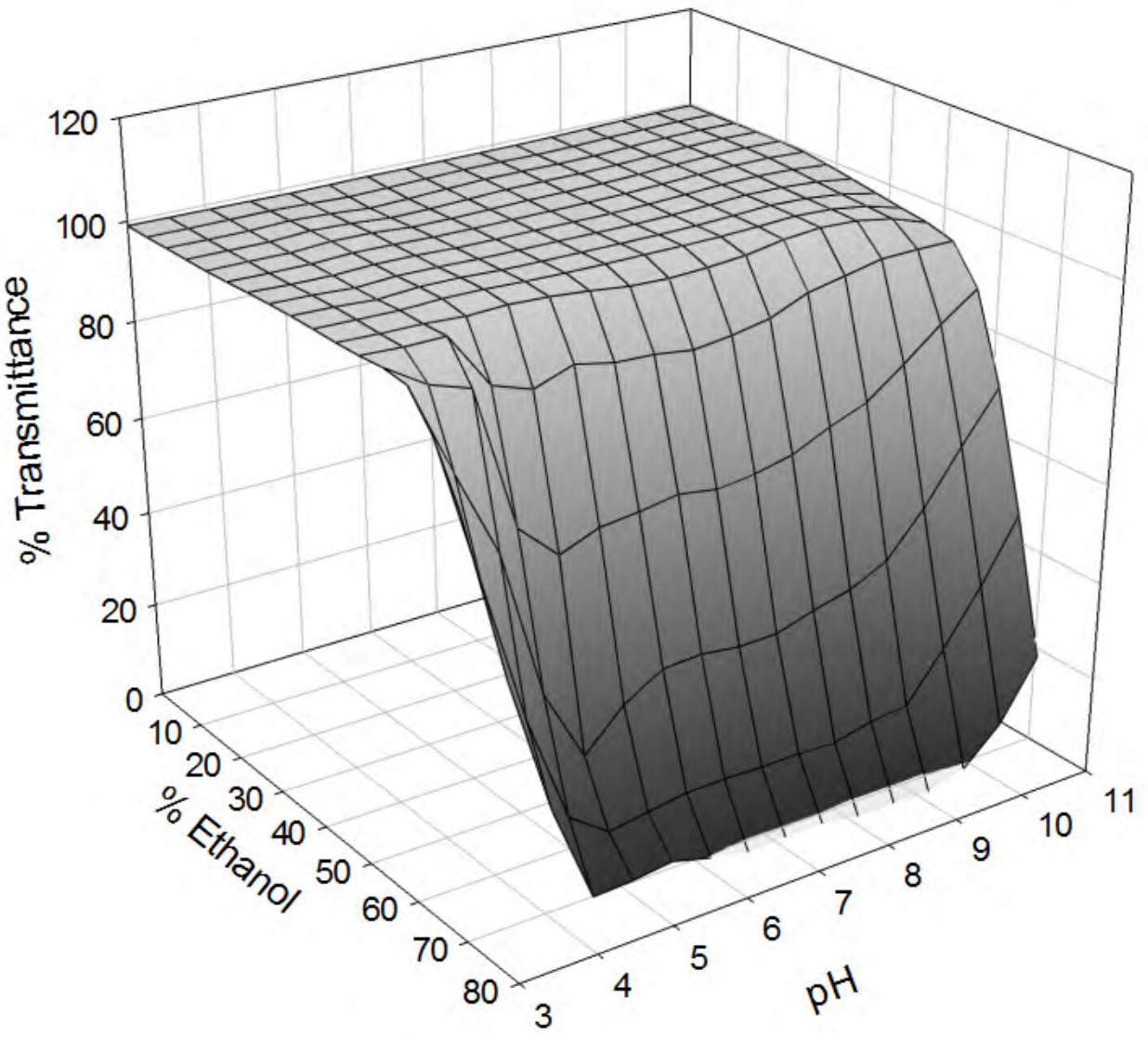


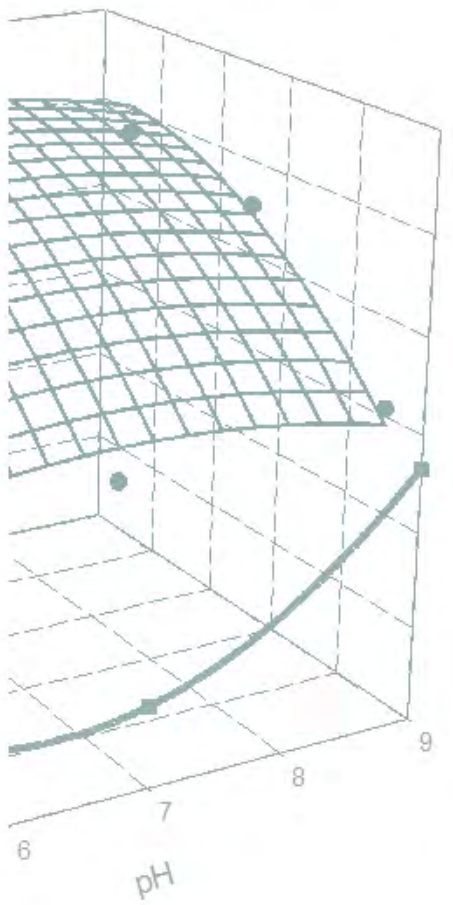
Storm et al., Geneva, 2006

Solubility: a physicochemical challenge

B225 gelatin with 0.5% w/v NaCl



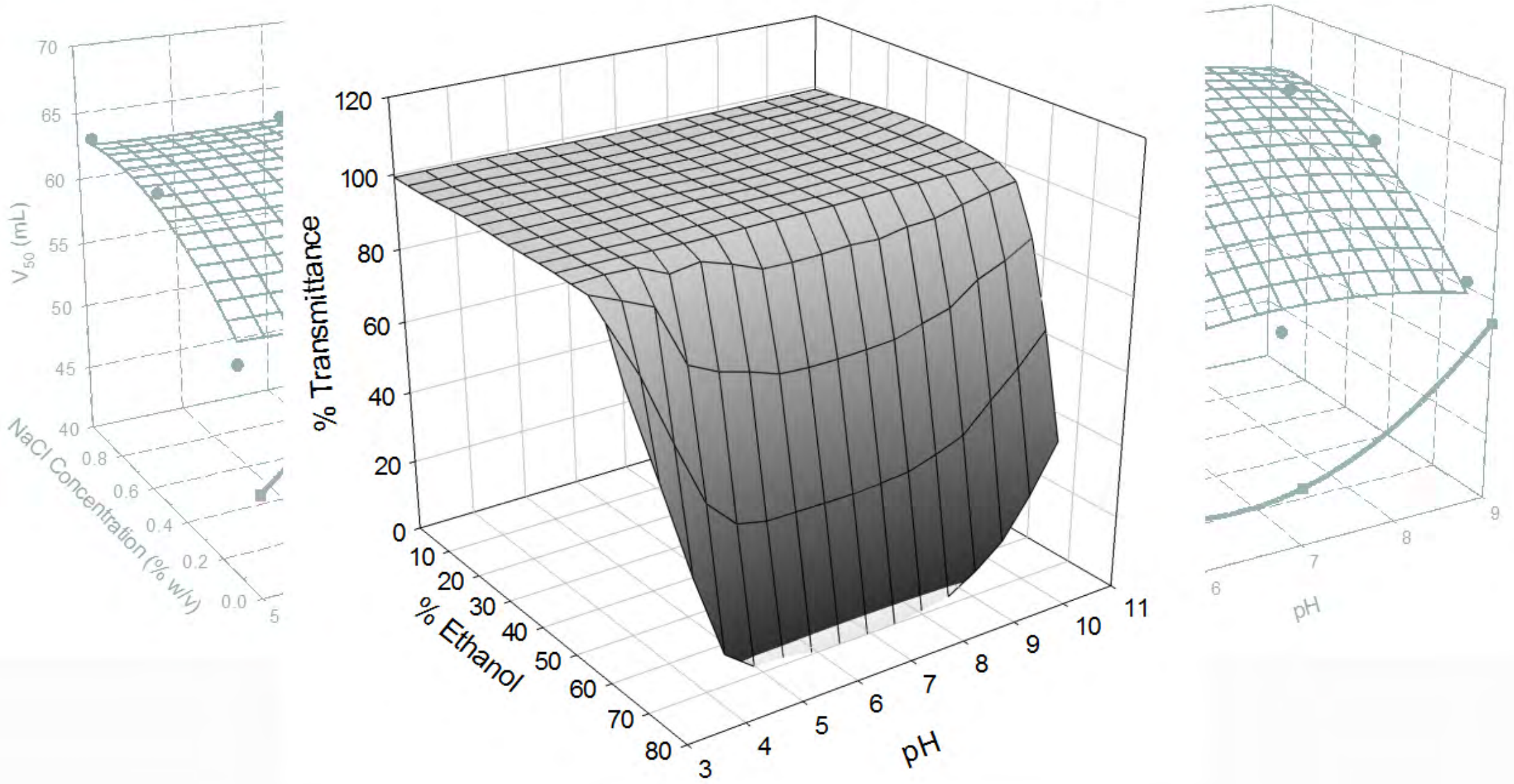




Storm et al., Geneva, 2006

Solubility: a physicochemical challenge

B225 gelatin with 0.9% w/v NaCl



Storm et al., Geneva, 2006

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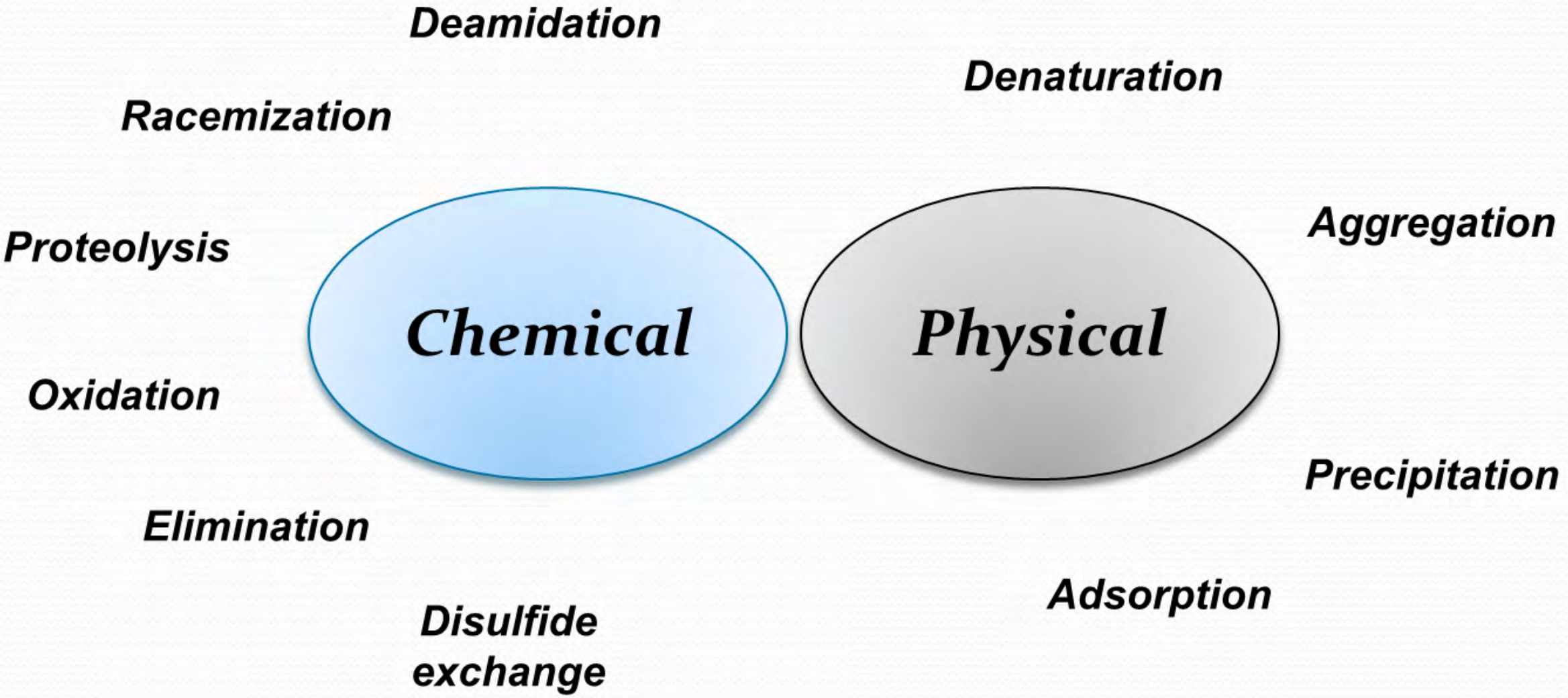
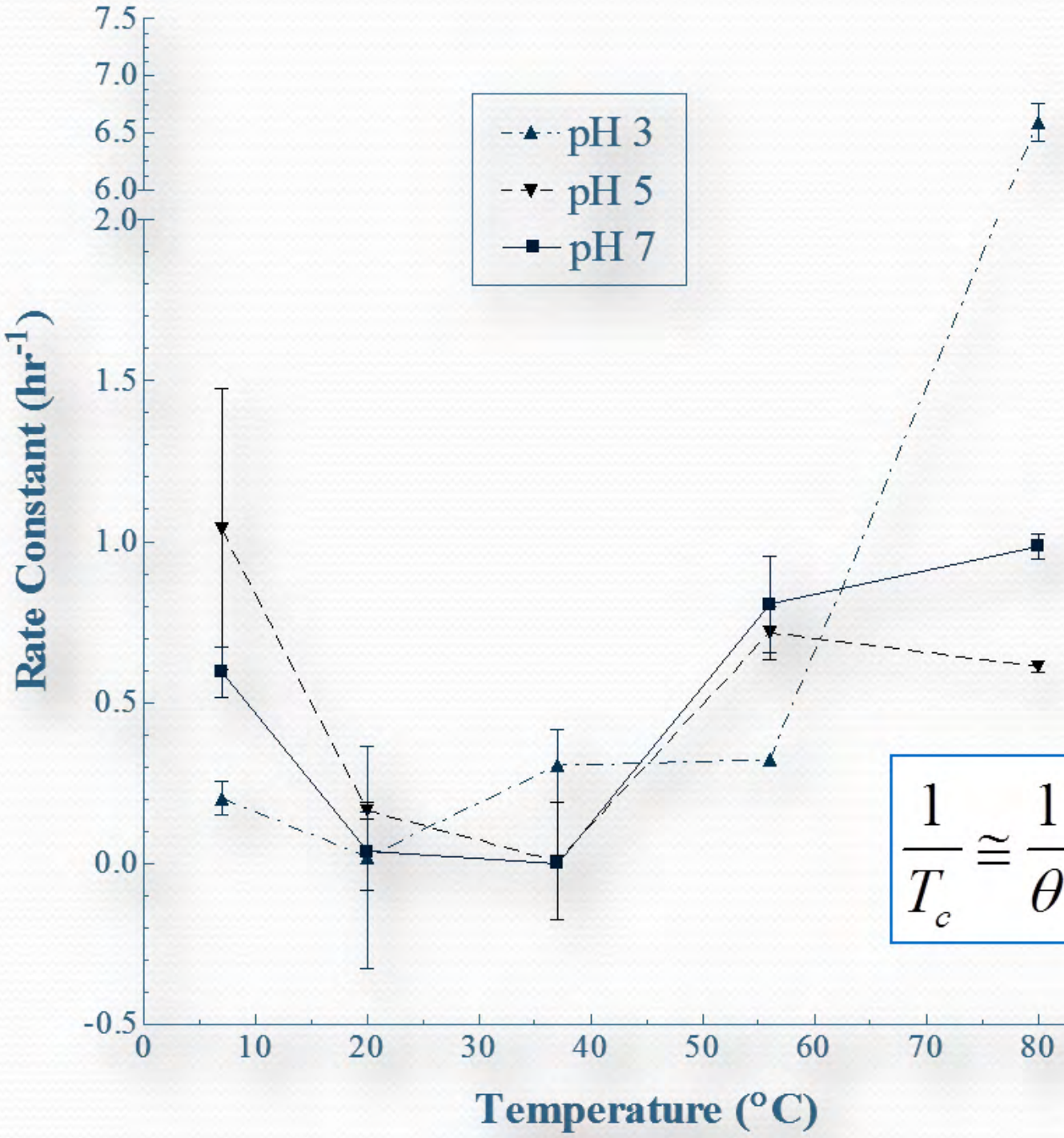
Formulation of protein-based drugs

The Stability Challenge

Chemical and physical stability



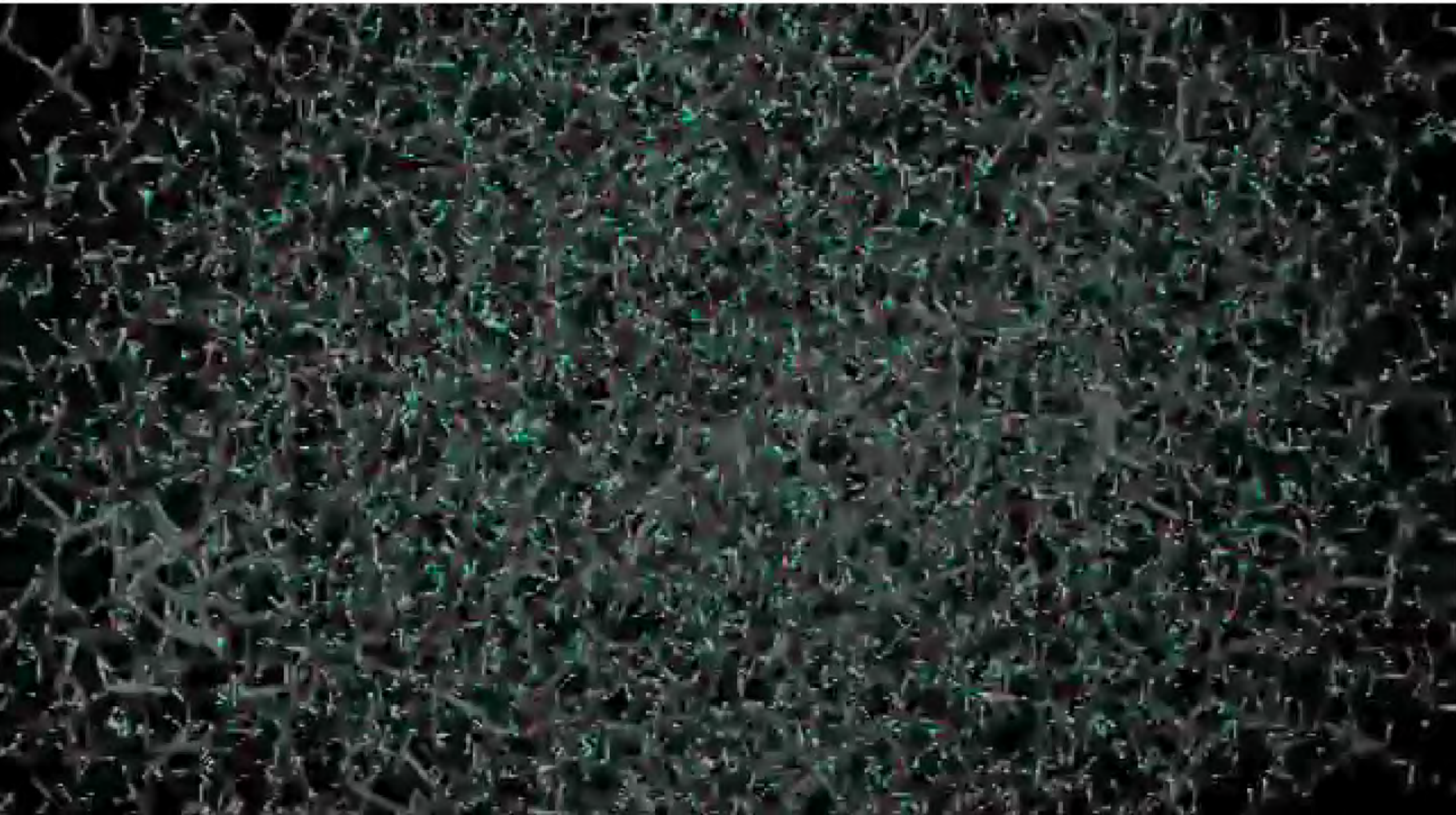
Denaturation and renaturation



$$\frac{1}{T_c} \cong \frac{1}{\theta}\left(1+\frac{D}{\sqrt{M}}\right)$$

Farrugia and Groves, 1999

Water: Friend or Foe?



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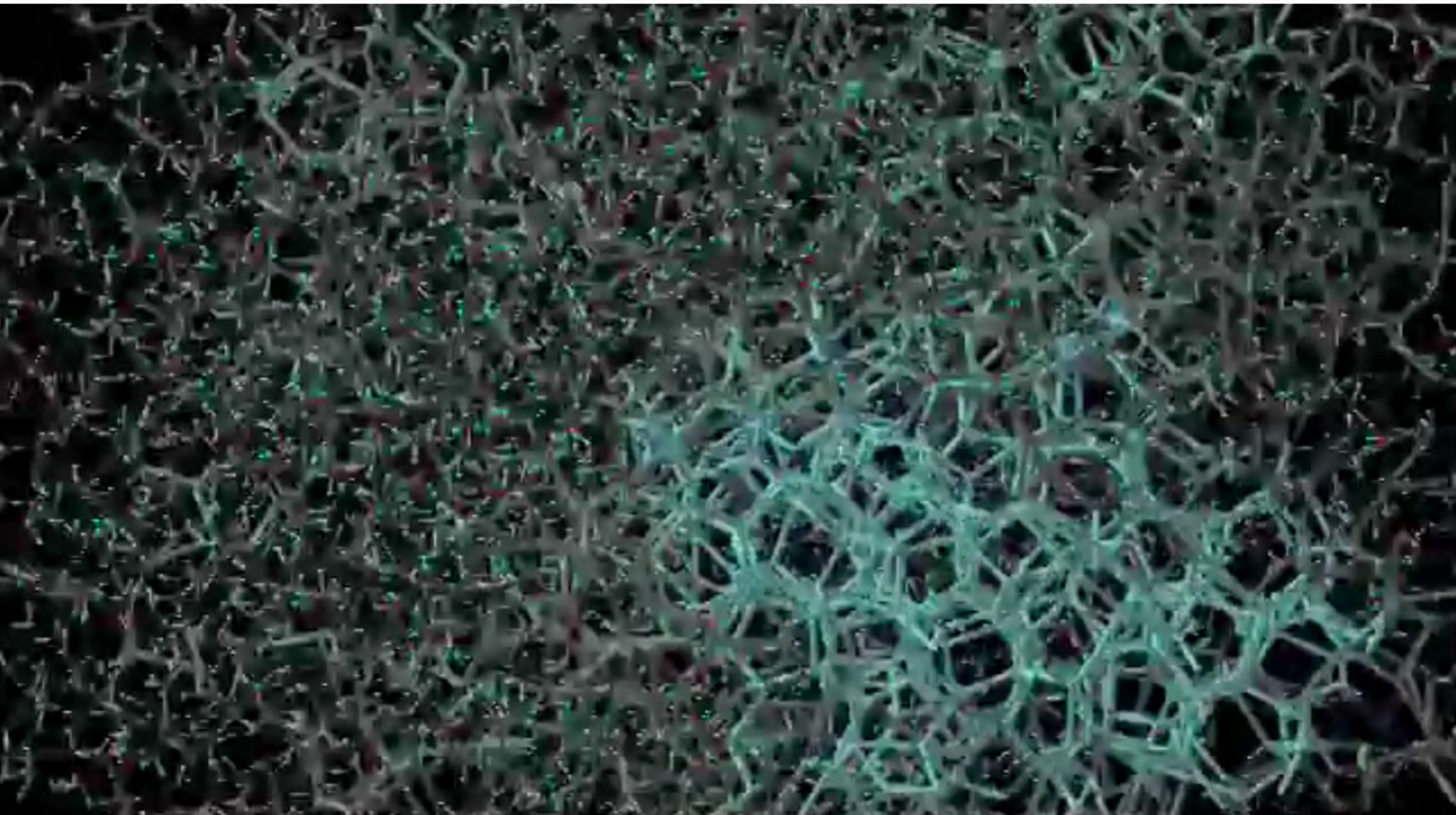

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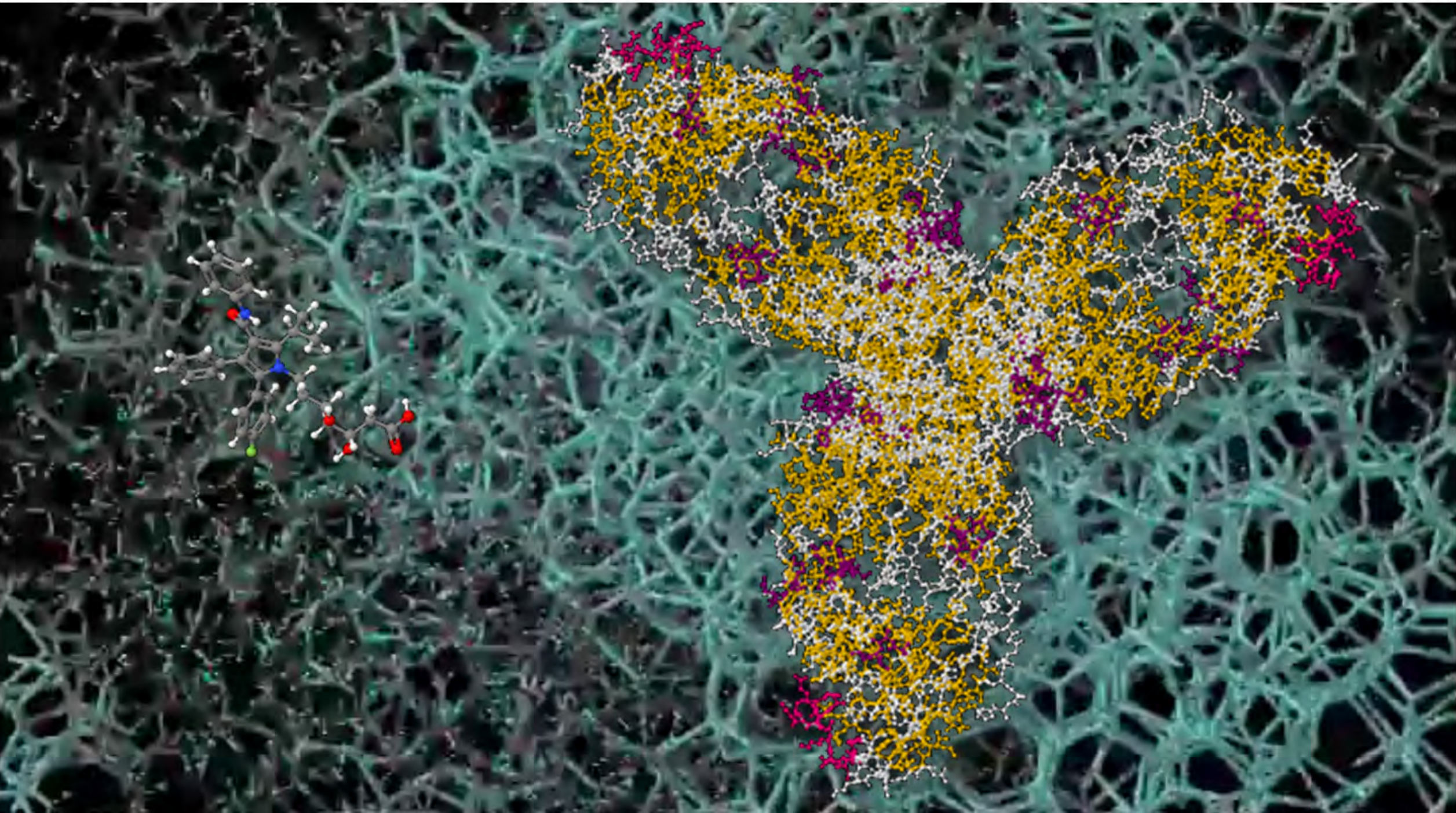
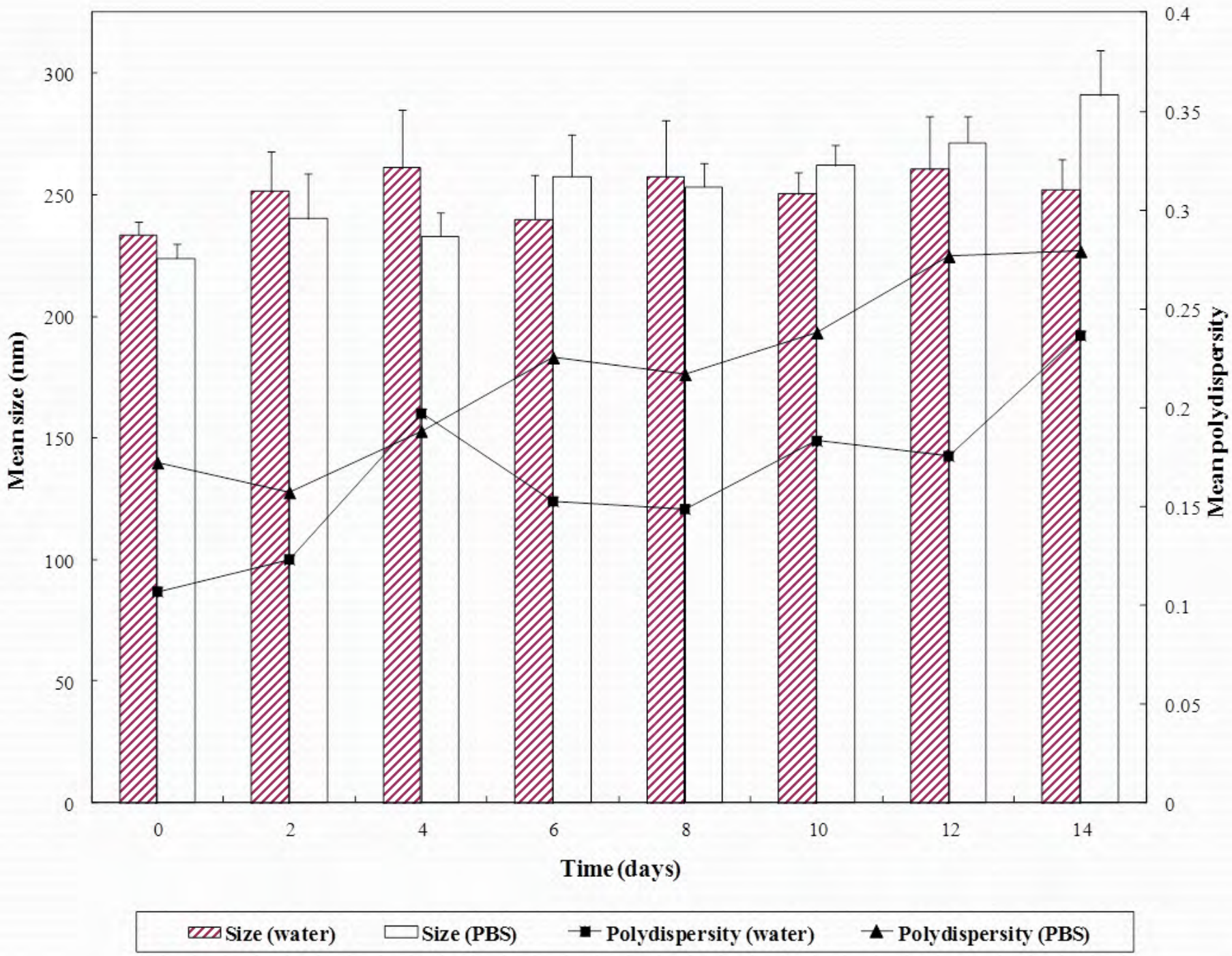


The stability challenge



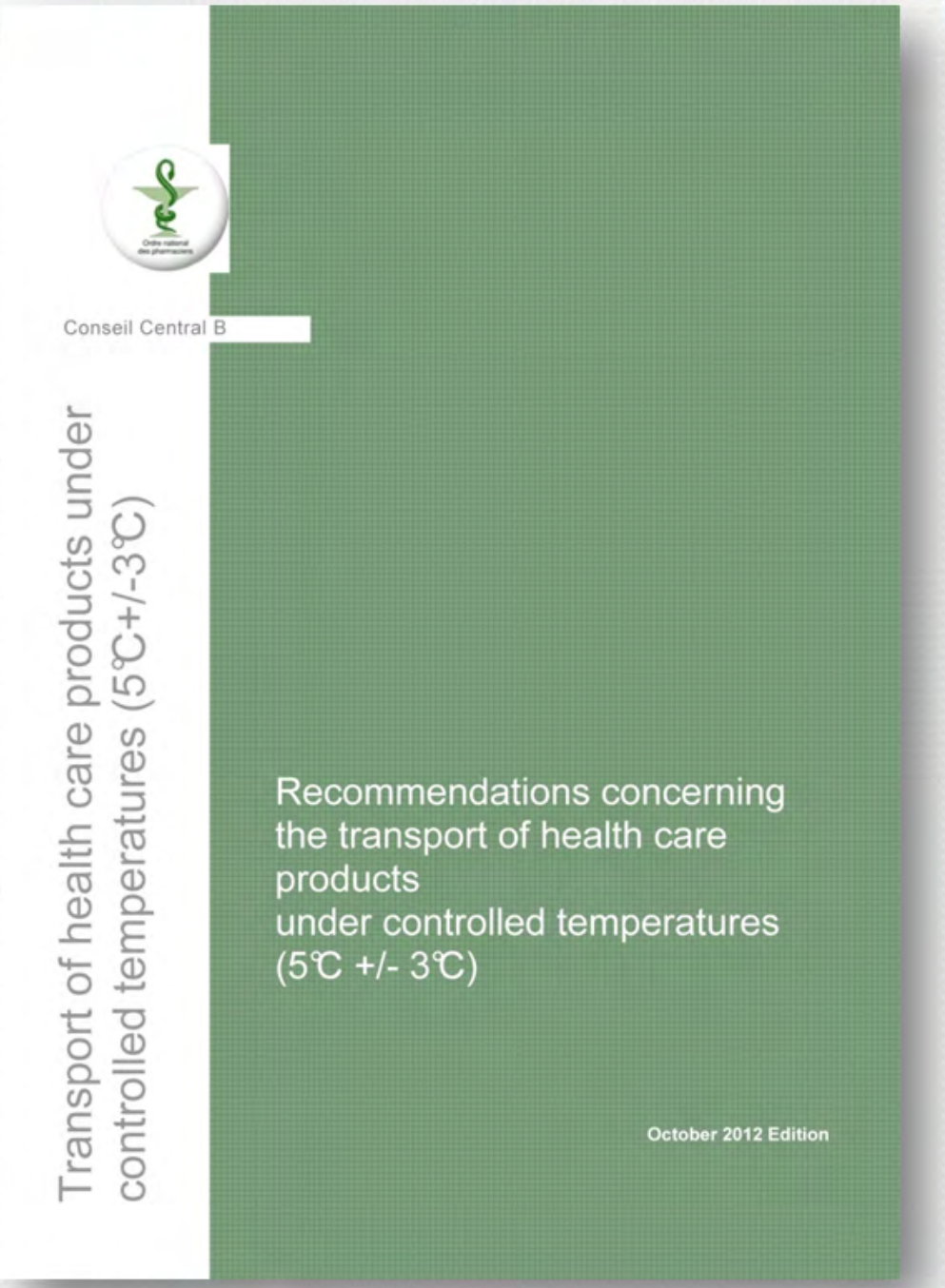
Farrugia, 1998

Formulation challenges

Issue	Challenges	Consequences & solutions
Addition of stabilizers, adjuvants or excipients	Novel components might be unproven in terms of safety or quality of raw ingredients	Additional regulatory scrutiny; use excipients of proven safety when possible
Introduction of novel production processes or novel equipment	Production facilities need to comply with cGMP	Additional regulatory scrutiny
Formulation development might be complex	Depends on whether a predictive rapid potency assay exists	Lack of preclinical models might increase clinical testing needed
Demonstrating clinical efficacy of reformulated product	Lack of validated clinical endpoints and biomarkers for many diseases	Longer larger clinical trials with clinical end points

Chen and Kristensen, 2009

Supply chain challenges (GDP)



Supply chain challenges (GDP)

- The carrier must constantly observe the official specification for the temperature of the health care products.
- The monitoring of the temperatures must be done through reliable calibrated measurement chains.
- The temperatures are monitored constantly. The recommended minimum frequency is 15 minutes but could be lowered to 2 minutes.
- The carrier must implement a real-time alarm system that allows him to detect any temperature problems.
- The carrier must ensure the traceability of the temperature through periods of handling of health care products belonging to the prime contractor.

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Thank you for your attention