

Sputter synthesis of antimicrobial materials and approaches to optimization of the process for deposition on web substrates.

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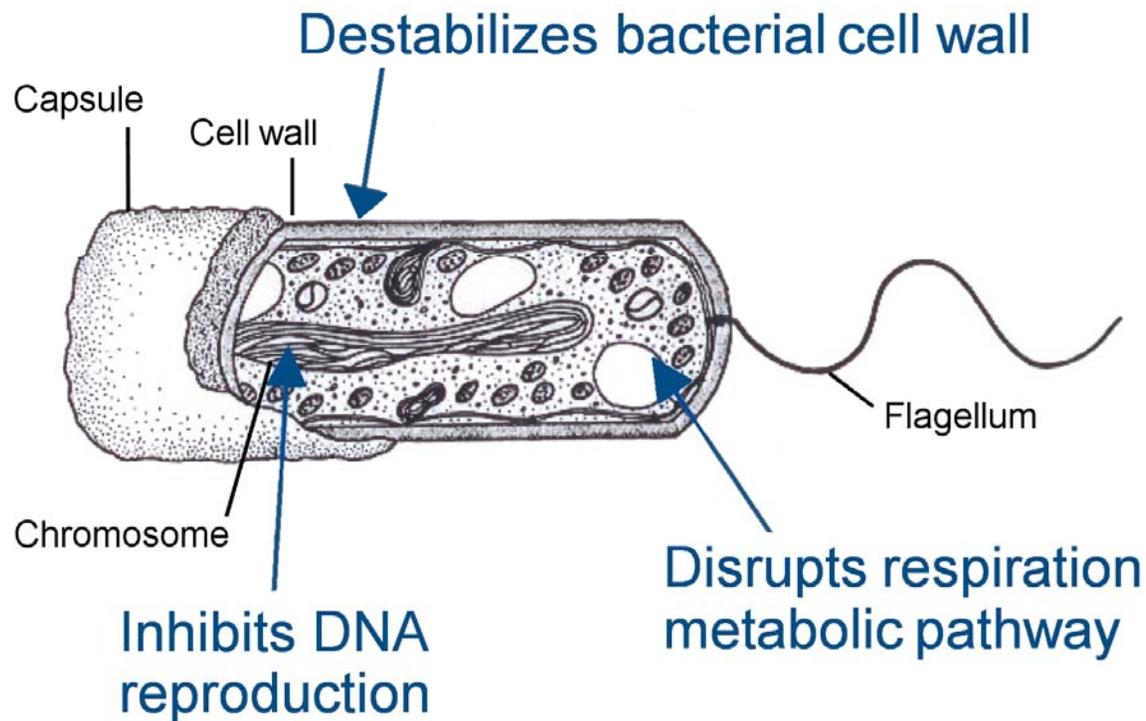


Brief History of Silver Use in Medicine

- Antiquity – Silver containers were used for food storage and silver coins were dropped into water as a disinfectant.
- 1884 – Dr. Crede, a German obstetrician, used a 1% silver nitrate solution to prevent blindness in newborns caused by post-partum infection from syphilis infected mothers.
- 1887 – Dr. von Behring used the same compound to treat typhoid and anthrax.
- 1964 – Dr. Moyer, of Washington University, used silver nitrate to treat infection in major burn wounds.
- 1968 – Dr. Fox, of Columbia University, brought silver sulfadiazine to medicine.
- 1998 – Sputtered nano-crystalline Ag dressings commercialized.

Why is Silver Effective as an Antimicrobial?

Silver attacks bacteria through multiple mechanisms whereas antibiotics generally work through a single pathway (and therefore are not effective against all bacteria).



Silver treatments are commonly used in burn wounds.

Traditional Silver Treatments

- **Silver Nitrate**

- Treatment involves application as a solution soaked gauze.
- Ag is depleted rapidly after administration, requiring frequent, painful dressing changes and giving highly variable silver concentrations in the wound.
- Ag_2NO_3 administrations are hypotonic.

- **Silver Sulfadiazine**

- Silver sulfadiazine was developed as both silver and sulfadiazine are known antimicrobials.
- It is applied in a cream format which needs frequent re-administration due to rapid silver depletion.
- Antibacterial efficacy is comparable to silver nitrate.
- Hypotonicity is not known to be an issue.

A Better Silver

An ideal silver technology would:

- I. Consistently deliver an appropriate level of active silver in a wound for a prolonged period.**
- II. Be effective against a broad host of bacteria**
- III. Not interfere with the wound healing process**
- IV. Require limited dressing changes that involve minimal disruption to the wound bed.**

Sputtered Nanocrystalline Silver Coatings

- In the 1990's extensive research was done on various ways to synthesize a silver coating to meet such criteria.
- Eventually, sputtering proved to be capable of producing a silver-based, nanocrystalline coating with the right characteristics.
- In contact with a moist wound the coating releases silver to levels sufficient to kill bacteria and maintains levels approximately constant for up to a week and beyond.
- Coating material can kill bacteria 4 times or more faster than silver nitrate or silver sulfadiazine.¹
- It is proven effective against:
 - over 150 bacterial strains
 - 9 clinical isolates of multiple antibiotic resistant bacteria including 'superbugs' such as MRSA and VRSA.²
 - 6 clinical fungal isolates including *candidas albicans*.²
- Currently, burn and chronic wounds comprise the majority of indications treated.

1. H. Yin, R. Lanford, R. Burrell, *J. Burn Care Rehab.*, 1999, **20**, 195.

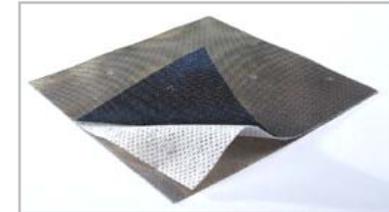
2. J. B. Wright, *et al.*, *Am. J. Infect. Control*, 1998, **26**, 572; *Ibid.*, 1999; **27**, 344.

Medical Devices for Wound Treatment - Dressings

Nanocrystalline silver coatings are deposited on a variety of web materials, depending on the primary aspect of the wound to be treated:

- **General wounds**

- Polyethylene mesh - relatively low melting point and low heat capacity.



- **Moisture control**

- Perforated polyurethane film (used with foam backing) - very thin, weak film.



- **Heavily exudating / cavity wounds**

- Calcium alginate - heavy, fibrous mat with low strength and high moisture content.



- **Conformable (improved handling / comfort)**

- Polyester mesh - stretchy material, which can be difficult to wind evenly and flat.



**Staying competitive in
the antimicrobial silver
market:
Process Optimization**

Substrate and Coating Considerations

Substrate Web:

- Some substrates have low softening point and low heat capacity.
- Many substrates are perforated / mesh and sputter-through can occur:
 - if drum-coating, material can build up on drum, possibly reducing thermal contact.
 - if free-span coating, inefficient substrate cooling.

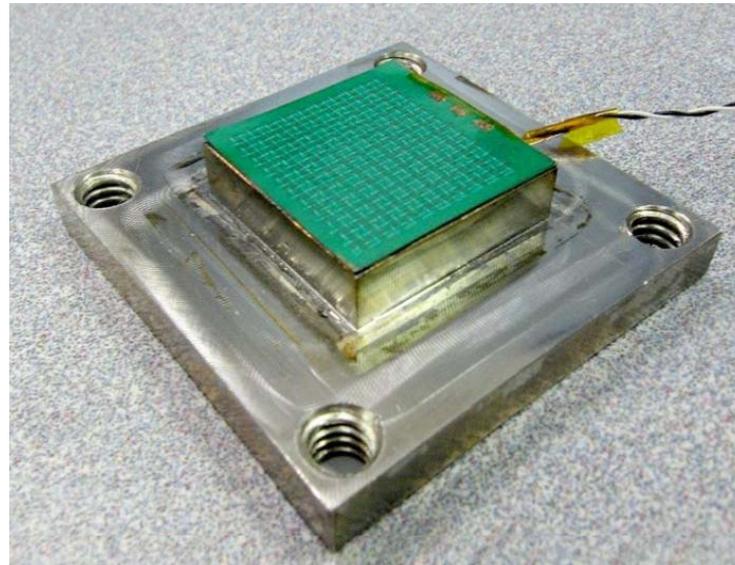
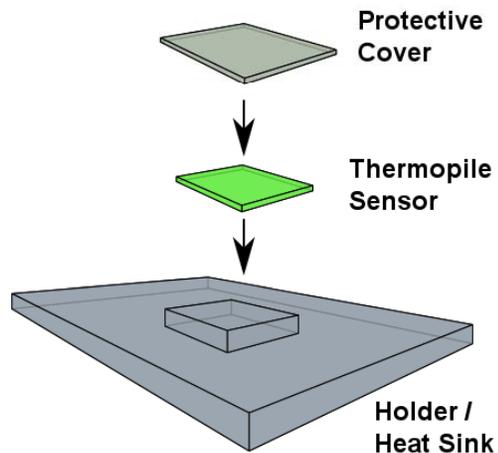
Coating:

- The coating is fairly thick (hundreds of nanometres) in order to provide sufficient silver.
- These nanocrystalline coatings can undergo re-crystallization at relatively low temperatures.

⇒ **Require a coating process with high deposition rate but low heat flux.**

Heat Flux Sensor

Heat flux is a major issue in this process, therefore it makes sense to try to measure it directly.



The above heat flux sensor arrangement was devised and found to successfully measure heat flux in a sputtering system.

Process Parameters

- The principal variables in the coating process are cathode current, process pressure and throw distance.
- Higher cathode currents, lower operating pressures, and shorter throw distances will generally all lead to higher deposition rates but also higher heat fluxes.
- The magnetic field of the magnetron, characterized by both its overall strength and its 'shape', can have a significant effect as well, adding to the complexity of the complete problem.

Approaches to Optimization:

- Typically, the 'traditional' approach would be to vary one parameter at a time.
- An alternative is to use a Design of Experiments (DOE) approach, particularly Factorial experiments. Typically:
 - 2 levels are used for each parameter.
 - Experiments are performed on all combinations of these two levels for each parameter (for n parameters this gives 2^n experiments).
 - Optionally, additional experiments may be carried out at the 'centre point', where all parameters are at their average level (this allows an assessment of the linearity of the response).

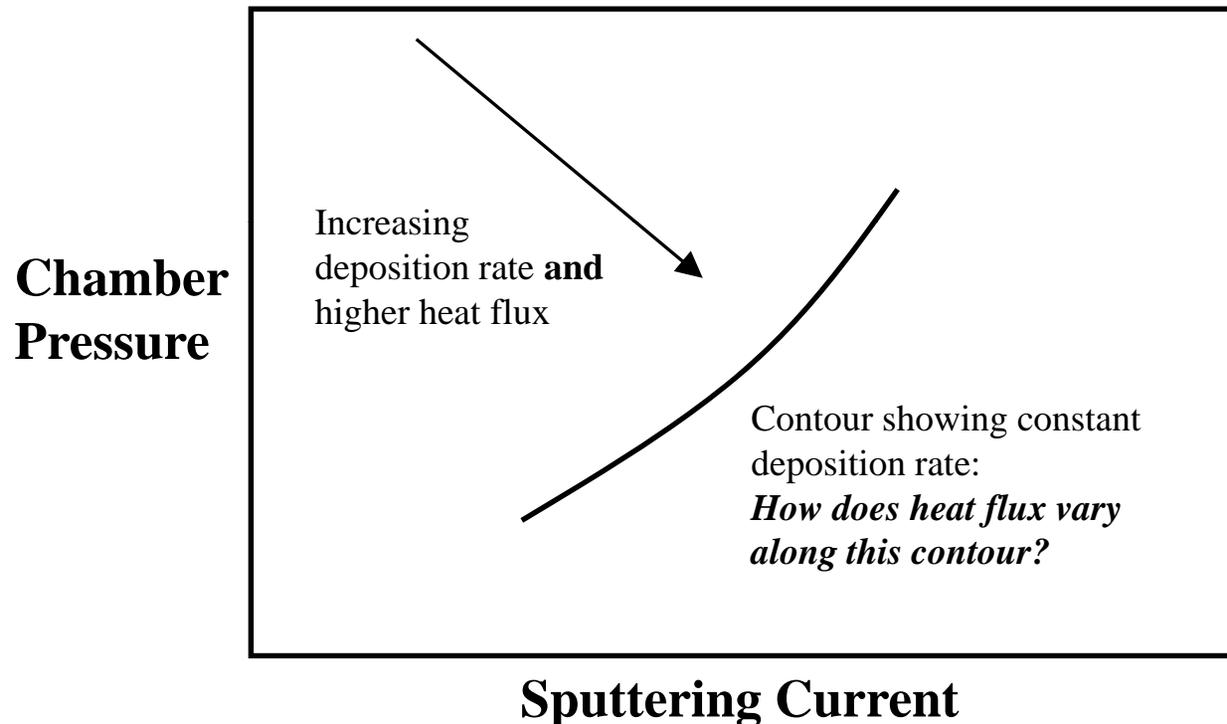
Advantages

- Less experiments (time, resource saving)
- Parameter interactions determined
- Better averaging of random variations

Disadvantages

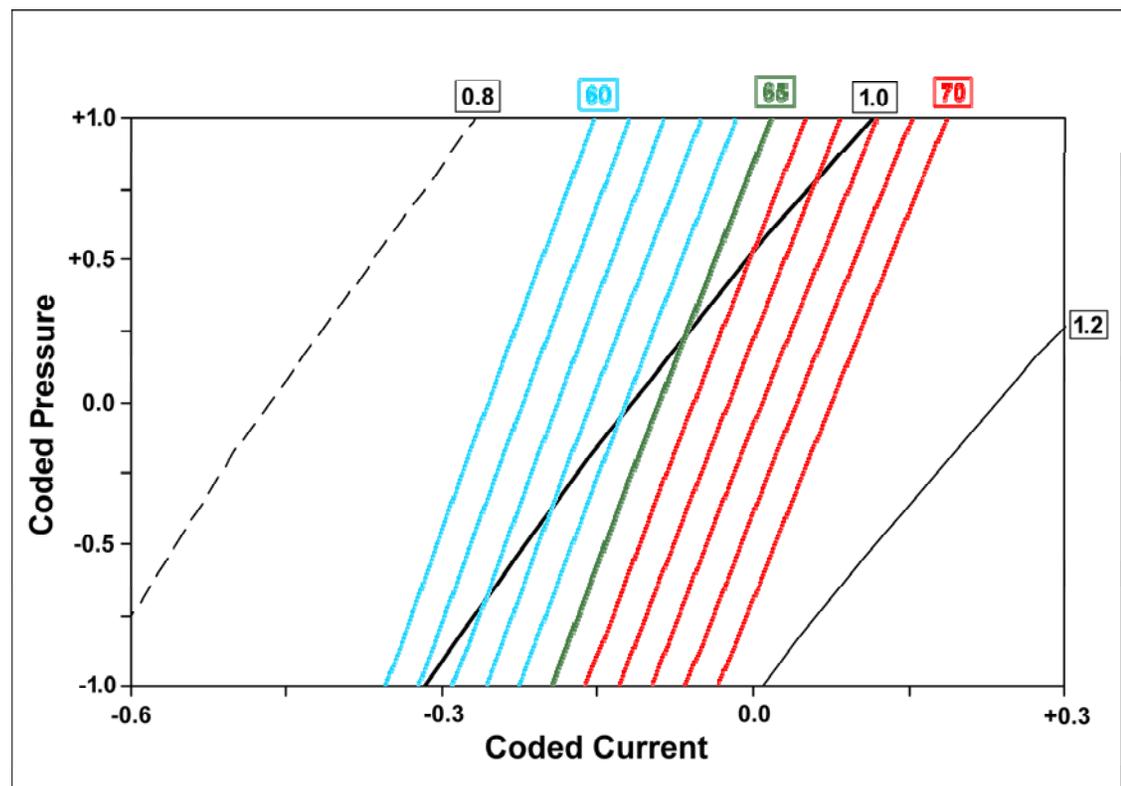
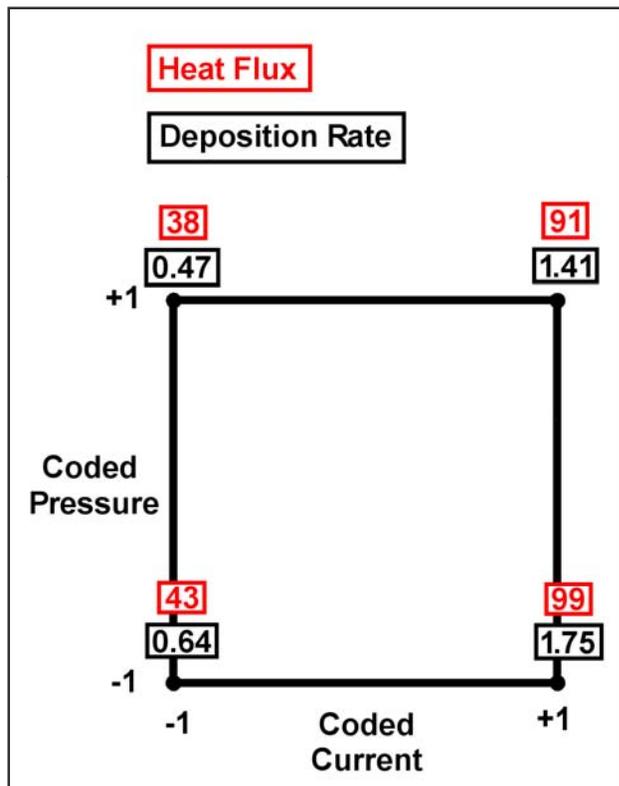
- Limited parameter range
- Linear response model
- Only works well with smoothly varying responses

Optimizing the Sputtering Conditions: Representative 2-D Example



- If other variables such as throw distance and magnetic field are added, the dimensionality of the problem increases. Furthermore, if reactive sputtering is used, chemical reactions will add further complexity.

Factorial Experiment: Deposition Rate and Heat Flux.



Future Outlook of Business

(OR...How to survive in tough financial times)

- Work on characterization, understanding and optimization of the process has helped to reduce production costs, improving profit margins and survivability, and continues to do so.

(Some results from this work have already been published and more will be published in the near future.^{3,4})

- Use of efficient research, development and optimization techniques, such as DOE, keeps research costs down while still offering production cost reductions and continued product development.
- Sputtering is a robust and unique process and there remains a lot of opportunities for novel films in the medical device arena.

3. D. Field, Proceedings - 51st. SVC Conference, April 19-24, 2008, Chicago (IL).

4. S. D. Ekpe; F. J. Jimenez; D. J. Field; M. J. Davis; S. K. Dew, J. Vac. Sci. Technol. A, **27**(6), *In press*.

Opportunities For Growth

- Significant opportunities still exist to grow high performance antimicrobial coatings:
 - New web materials for different wound aspects.
 - Coating of other medical devices (e.g. implants).
- Sputtered nanocrystalline silver can be converted to a powder for incorporation into creams, gels, etc.
- Coatings have also been shown to have anti-inflammatory properties,⁵ which can be helpful in the healing of wounds and treatment of other conditions.
- Sputtering can be used to deposit nano-structured coatings with other properties of bio-medical interest (e.g. wear resistance).

5. K. C. Bhol, *et al.*, *Clin. Exp. Dermatol.*, 2004; **29**, 282 and *Br. J. Dermatol.*, 2005, **152**, 1235.

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 - Dr. Samuel Ekpe²
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1: NUCRYST Pharmaceuticals
2: University of Alberta, Canada