



SR-XRD *in situ* monitoring of copper-IUD corrosion in simulated uterine fluid using a portable spectroelectrochemical cell



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ABSTRACT

The objective of this work is to study the initial corrosion of copper in the presence of gold when placed in simulated uterine fluid in order to better understand the evolution of active components of copper-IUDs. In order to carry out this study, a portable cell was designed to partially simulate the uterine environment and provide a way of tracking the chemical changes occurring in the samples *in situ* within a controlled environment over a long period of time using synchrotron spectroelectrochemistry. The dynamically forming crystalline corrosion products are determined *in situ* for a range of copper–gold surface ratios over the course of a 10-day experiment in the cell. It is concluded that the insoluble deposits forming over this time are not the origin of the anticonception mechanism.

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1. Introduction

Copper-bearing intrauterine devices (IUDs) are a very popular method for long-acting reversible contraception (LARC). The release of copper ions into the fluid medium of the uterus and their reaction with the endometrium reduces the probability of fertilization and implantation [1,2]. It has been stated that the primary source of these ions is cuprite (Cu_2O) formed on the device surface through *in utero* corrosion with the uterine environment [3–5]. Recent work by Palmer [6] shows that cuprite has very low solubility at the pH and temperature of the uterine fluid so this seems unlikely especially when far more soluble compounds such as copper sulfate and chloride may also be formed. However, without studying the reactions *in situ*, one can never be certain what surface condition gives rise to the release of copper ions. Known copper chemistry suggests that treatments such as rinsing of removed *in utero* samples and storage

prior to analysis would provide misleading results through, for example, hydrolyzation of compounds such as nantokite (Cu(I)Cl) [7,8], rinsing away of soluble copper compounds (CuCl_2 , CuSO_4 , etc.) and removal of non-adherent insoluble material such as colloidal sulfides.

A new generation of frameless IUDs (Gynefix®, Contrel Research, Ghent, Belgium) aims to reduce the side effects of conventional IUDs such as bleeding, pain and expulsion [5]. The addition of gold to these devices [9] should accelerate the copper release [10–12] and therefore improve anticonception rates for a smaller device, and possibly provide protection against sexually transmitted diseases (STDs) [13–16]. A galvanic corrosion reaction, due to the electropotential difference between the metals, is induced when copper is in contact with the more noble gold [17]. In this bimetallic system copper (which has the lower electrode potential) acts as a sacrificial anode, hence promoting faster copper corrosion.

In our experiments, samples modeling this Cu/Au system resided within a portable cell for one week while *in situ* data were collected. Samples were made with three differing surface area ratios of Cu/Au in order to study the effect of increased Cu/Au contact on corrosion *in utero*. The corrosion potential (E_{corr}) was recorded continuously to monitor the electrochemical behavior of one sample.

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2. Material and methods

Experiments were carried out within a heated portable cell to partially simulate the uterine environment. Three samples with differing surface area ratios of Cu/Au were used. Polished copper coupons of 12.5 mm diameter (99.99%, Goodfellow, Cambridge) were sputter-coated with gold using a JEOL JFC-1300 Auto Fine Coater. Coupons were covered with copper tape masks to create samples with 3 different sizes of gold spot – one sample reproduced the Cu/Au surface area ratio of the Gynefix® (2.83 mm diameter Au, Sample 1), and the others had higher (6.25 mm diameter Au, Sample 3) and lower (1.5 mm diameter Au, Sample 2) ratios. Masked coupons were then sputtered at 30 mA for 600 s to deposit 100 ± 50 nm of gold (see Supporting Information, Fig. S-1).

The portable cell [18] is of the Bragg-type. It is a multiple cell with a three-sample (i.e. three working electrode) capacity (Fig. 1). It is cuboid in shape (dimensions: $190 \times 75 \times 70$ mm). The three samples are moved between surface analysis and electrochemical/environmental exposure positions (~ 100 μm and 10 mm thick electrolyte layers respectively) using a stepper motor, which drives three worms on a common shaft. The worms (part 8, Fig. 1) drive the cams (part 7, Fig. 1) of the working electrodes [19] synchronously through the worm wheels (part 9, Fig. 1). The rotation of the shaft can be remotely controlled from outside the experimental hutch of a synchrotron. By this means the sample can be analyzed with a lower energy more surface specific X-ray beam than is the case with a Laue cell, and the cell can be used for X-ray absorption spectroscopy as well. The hardware is easily adapted for use on different beam lines.

The portable cell functions as a three-electrode electrochemical cell and uses custom made working and Ag/AgCl reference electrodes as previously described [20]. A 1 mm diameter platinum counter electrode stretches along one of the long sides of the cell, adjacent to the working electrodes. The electrode is attached to the outside of the cell through a small Pt connection block and a length of 1 mm diameter wire (part 5, Fig. 1). Further design specifications for the portable cell can be found in the Supplementary Information.

The corrosion potential (E_{corr}) is monitored using a modified voltage data logger (Matchtech Volt 101A, USA). The working electrode output and reference electrode are attached to the voltage logger. This device was chosen for its portability and voltage detection range (± 3 V). However, the input impedance of the device had to be buffered to account for the high output impedance of the portable cell. The output impedance of the cell's electrode system was measured using aqueous electrolyte and found to be 375 k Ω . The voltage logger was buffered to 300 M Ω with a purpose built high input impedance amplifier to ensure that it did not shunt the cell.

E_{corr} data was collected every 1 s from Sample 1 by the data logger for the duration of the experiment.

For shorter measurements and not during transportation, a Palmsens handheld potentiometer (Palmsens BV, The Netherlands) can alternatively be used. This device can conduct a wider range of electrochemical measurements, such as cyclic voltammetry and chronopotentiometry at the working electrodes to collect other electrochemical data [21].

Samples were mounted within the cell two days prior to beam time as the most interesting behavior is said to occur in the first week [22,23]. The cell body was flooded with a simulated intrauterine fluid (SUF) as described by Bastidas et al. [4] and a custom cartridge heater was used to keep samples at body temperature (37 °C) during the experiment. SUF contains calcium, potassium and sodium chlorides (0.167, 4.97 and 0.224 g/l respectively), urea (0.48 g/l), glucose (0.5 g/l), monosodium phosphate (0.072 g/l), sodium bicarbonate (0.25 g/l) and albumin (35 g/l) – SUF has no associated biological hazard and has a pH of 6.2 [4].

When it was not being transported, heated electrolyte from an external reservoir was circulated through the cell by a peristaltic pump (Watson Marlow 502S) from a regulated hotplate (ESK Hei-Con, Heidolph Instruments, Germany) at 5.5 mL/min flow rate to allow slow and uniform flow into the cell.

SR-XRD patterns were obtained from these samples *in situ* at time intervals of approximately 24 h for 5 days. These were collected using a Mar CCD 165 (Mar USA Inc.) 2D detector at XMaS (station BM28,

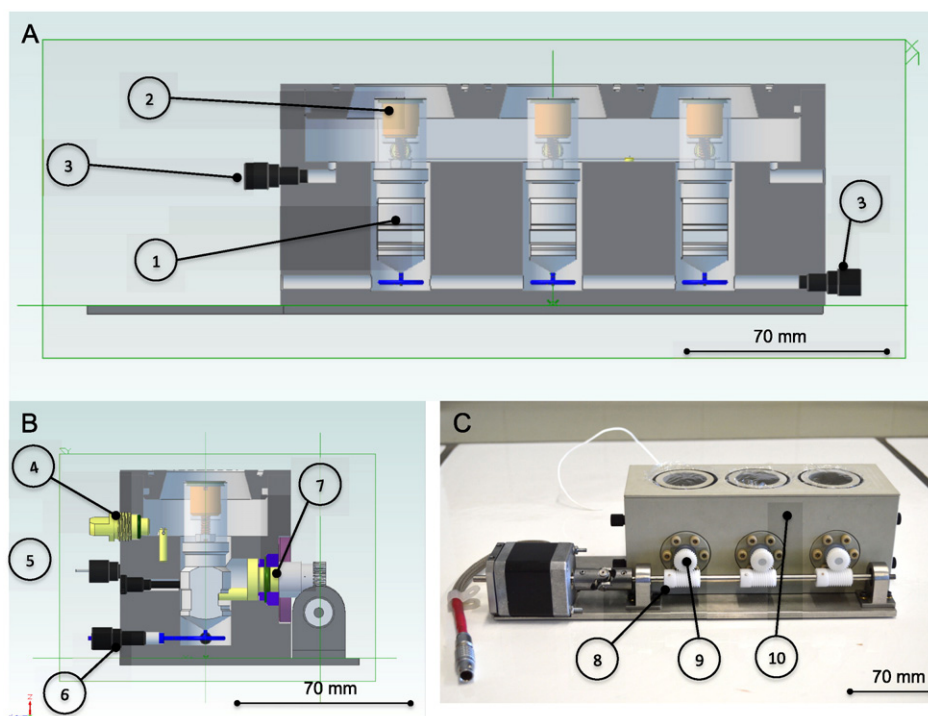


Fig. 1. 3D drawings of the portable cell (XZ plane – A; YZ plane – B) and the assembled cell, with motor (C). Parts shown are the piston (1), working electrode (2), electrolyte filling ports (3), M12.5 \times 1.25 ports (4), counter electrode outlet (5) working electrode outlet (6), cam assembly (7), worm (8), worm wheel (9) and cell body and window (10).

ESRF). The camera was mounted at 44.5° to the incident X-ray beam with a detector-sample distance of 132 mm. X-rays with an energy of 8 keV were incident at 10° to the surface into a footprint of $3 \times 0.5 \text{ mm}^2$. Diffraction patterns were collected using an exposure time of 10 s and the beam was shuttered between patterns to minimize sample damage and radiolysis. A total of 9 2D patterns was recorded at 0.5 mm intervals along a line within a range of $\pm 2 \text{ mm}$ from the center of each sample across the copper-gold boundary (see Fig. S-2 for example raw diffraction patterns). The data processing was carried out using the esaProject software [24]. A webcam mounted above the cell was used to record images of the samples.

3. Results and discussion

3.1. Monitoring the corrosion of copper *in situ*

Fig. 2 shows the internal temperature of the cell as a function of time. Readings were taken manually whenever there was access to the hutch and the temperature controller. The temperature dropped below 36 °C only during the setting up of the experiment when the cell was initially removed from its insulated transportation box. However once electrolyte pumping was restarted body temperature was reinstated over the course of 2 h and remained within range for the rest of the experiment.

Fig. 2 also shows E_{corr} of Sample 1 during the entire experiment. The E_{corr} has been recorded at -0.2 V for similar experiments with copper in this electrolyte [25], which shows the multiple cell setup is not adversely affecting the detection of electrochemical data from individual samples. From the start of the experiment until day 7, the E_{corr} steadily decreased to approximately -0.1 V from 0.1 V showing steady corrosion of the working electrode surface. The increase in E_{corr} after day 7 demonstrates passivation of the electrode surface. Complementary *in situ* surface analysis (described below) supports this result.

The individual XRD patterns recorded across the copper-gold boundary were summed to produce a set of 5 average images for each sample. In this way, the main differences between the three samples with increasing Cu/Au surface area ratios (and therefore increasing amounts of Cu/Au contact) could be observed. Fig. 3 shows the data obtained over the course of the 5-day synchrotron experiment.

Sample 1 had the intermediate Cu/Au ratio. Fig. 3 shows that it had started corroding measurably by day 3 of the experiment. Over the following four days the main products observed were cuprite (Cu_2O) and copper (I)/(II) sulfides. From day 6, crystalline sodium chloride was

also detected, having crystallized out of the SUF electrolyte. Thick, flaky cuprite crusts have been observed previously [3–5] during *ex situ* analysis. The formation of copper sulfides has been tentatively suggested elsewhere [26] but this is the first time they have been observed *in situ* immersed in SUF. Sulfide salts were not added to the SUF, so it is presumed the source of sulfide ions is albumin which is known to contain disulfide bonds [27].

The concentration of each species on the surface is unknown but from the E_{corr} data we can infer that passivating cuprite becomes the dominant species during the experiment, after the initial corrosion of the surface.

Sample 2 contained the least amount of gold on its surface and therefore the least Cu/Au contact. On day 4, copper (I)/(II) sulfides had already formed. On day 6 nantokite (CuCl) was also detected as well as sodium chloride directly from the SUF. Nantokite has been previously observed at this pH [4,25] and originates from the reaction of copper with chloride ions in solution [8,28]. However, no cuprite was observed. Previous work has shown that in aqueous solution at pH 6.5 a continuous conversion of nantokite to cuprite by hydrolyzation is expected [8,28]. On Sample 1, cuprite was already seen on day 3. It appears that a lower amount of Cu/Au contact on Sample 2 delays the formation of cuprite, a more advanced corrosion product.

By day 7, nantokite still remained on the surface, no cuprite was observed, and sulfides were detected at 3.75 \AA^{-1} and 4.5 \AA^{-1} . It is also possible that the copper (I)/(II) sulfides remained on the surface in an amorphous state as it has been noted previously [29] that the experimental conditions determine the phase in which copper sulfide is formed [30–33].

Sample 3 had the most gold on its surface and therefore the largest Cu/Au contact area. No crystalline corrosion products were detected until day 7 when a range of copper (II) species was observed: CuCl_2 [4], CuO [1] and CuS [26]. These compounds have a range of solubilities in water: CuCl_2 is very soluble (76 g/100 ml at 25 °C), whereas CuO and CuS are both insoluble. It is possible that the CuCl_2 was formed before 7 days, had dissolved immediately and was a source of Cu^{2+} ions in solution. In other words, after 7 days the galvanic corrosion rate had increased due to the large Cu/Au contact area and the CuCl_2 was being formed faster than it could dissolve. In addition calcite [3,4] and aragonite (CaCO_3 polymorphs) had been deposited from the SUF.

The results from the XRD are backed up by visual observations as shown in the supporting information (Fig. S-1). The surfaces of Samples 1 and 2 were covered with a black powdery layer between day 4 and 5, which was loosely attached to the surface initially and was easily removed when simply moving the working electrode within the cell. However, towards the end of the experiment and upon removal of the samples, this layer was more permanently attached to the surface. Sample 3 showed a black ring only around the gold spot but this did not appear until the final days of surface analysis, leaving a copper surface almost free of visible corrosion. It is clear from these data that there is a difference in the corrosion behavior of the three samples in SUF, which is dependent on the contact between gold and copper: the greater the Cu/Au contact, the more advanced the corrosion.

4. Conclusion

Using a novel portable multicell, we were able to record SR-XRD patterns from three different samples every 24 h for 5 consecutive days during which time the temperature of the cell was also monitored. The cell was successfully transported to the beamline without losing heat or electrolyte whereupon surface analysis could commence. Gold promotes copper corrosion when they are in contact. Our results clearly demonstrated the effect of increased Cu/Au contact on corrosion *in utero*: the more copper-gold contact, the more advanced the corrosion.

This work highlights the importance of techniques which monitor corrosion processes *in situ*. The contraceptive action of copper depends on the copper ion release, and the sequestering of copper ions in

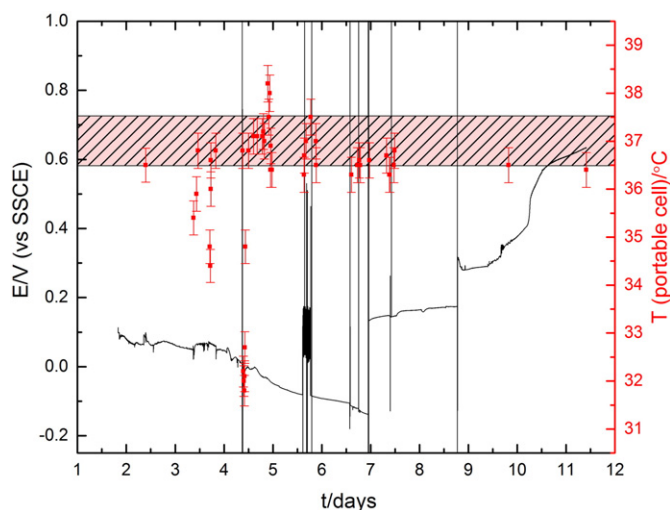


Fig. 2. The E_{corr} and temperature of the cell during the experiment. The red shaded area indicates body temperature, the target temperature range. Days 1, 2, 8 and 9 were set-up and transportation days to and from the ESRF. Days 3–7 were experimental time at the XMaS beamline.

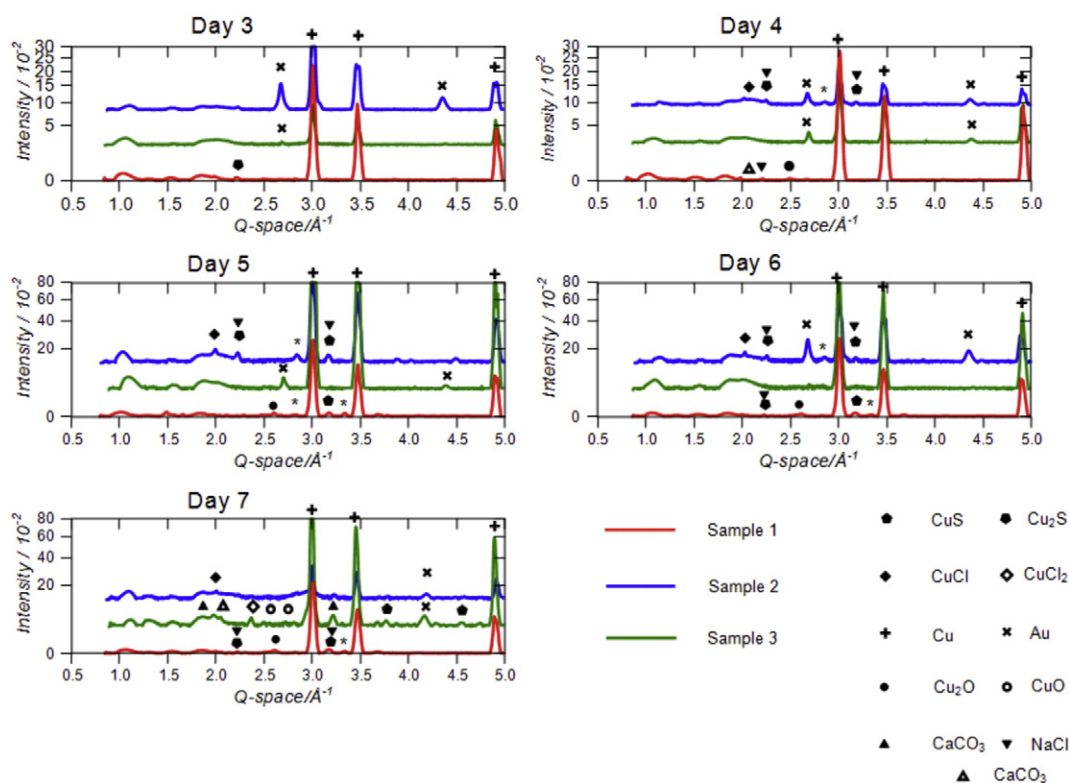


Fig. 3. Summed diffraction patterns from across a 4 mm range on the surface of the Samples 1–3 for five consecutive days. Corrosion products are labeled as shown. Unidentified peaks are marked with a *.

insoluble corrosion products does not seem likely to contribute to this end. On the other hand, the observation of CuCl_2 on the sample with the most gold, combined with the lack of insoluble products suggests this as a significant source, probably in all cases.

Experiments now need to be carried out on a longer timescale (months to years) in order to probe ongoing copper corrosion in this medium and to further test the capabilities of the portable cell concept, for example the use of other spectroscopic techniques such as XAS, Raman and IR to probe the sample surface and the electrolyte *in situ*.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.bioelechem.2016.02.014>.

References

- [1] K.M. Lewis, R.D. Archer, A.P. Ginsberg, A. Rosenzweig, The corrosion chemistry of copper intrauterine devices, *Contraception* 15 (1977) 93–104, [http://dx.doi.org/10.1016/0010-7824\(77\)90041-5](http://dx.doi.org/10.1016/0010-7824(77)90041-5).
- [2] E. Chantler, Copper loss from Copper IUDs, *Intrauterine Contraception: Advances and Future Prospects* 1984, pp. 198–210.
- [3] J.M. Bastidas, E. Cano, N. Mora, Copper corrosion-simulated uterine solutions, *Contraception* 61 (2000) 395–399.
- [4] N. Mora, E. Cano, E.M. Mora, J.M. Bastidas, Influence of pH and oxygen on copper corrosion in simulated uterine fluid, *Biomaterials* 23 (2002) 667–671.
- [5] D. Wildemeersch, P.-J. Sabbe, M.G. Dowsett, V. Flexer, P. Thompson, D. Walker, et al., Assessment of copper corrosion from frameless copper IUDs after long-term in utero residence, *Contraception* 90 (2014) 454–459, <http://dx.doi.org/10.1016/j.contraception.2014.05.009>.
- [6] D.A. Palmer, Solubility measurements of crystalline Cu_2O in aqueous solution as a function of temperature and pH, *J. Solut. Chem.* 40 (2011) 1067–1093, <http://dx.doi.org/10.1007/s10953-011-9699-x>.
- [7] R. Grayburn, M. Dowsett, M. Hand, P.-J. Sabbe, P. Thompson, A. Adriaens, Tracking the progression of bronze disease – a synchrotron X-ray diffraction study of nantokite hydrolysis, *Corros. Sci.* 91 (2015) 220–223, <http://dx.doi.org/10.1016/j.corsci.2014.11.021>.
- [8] I.D. Macleod, Bronze disease: an electrochemical explanation, *Bull. ICCM.* 7 (1981) 16–26.
- [9] R. Gonen, L. Gal-Or, A. Zilberman, M. Scharf, A copper-based intrauterine device with gold or platinum core: *in vitro* and *in vivo* studies, *Contraception* 24 (1981) 657–671.
- [10] C. Goh, W. Chong, T. Lee, C. Breach, Corrosion study and intermetallics formation in gold and copper wire bonding in microelectronics packaging, *Crystals* 3 (2013) 391–404, <http://dx.doi.org/10.3390/cryst3030391>.
- [11] F.U. Renner, A. Stierle, H. Dosch, D.M. Kolb, T.-L. Lee, J. Zegenhagen, Initial corrosion observed on the atomic scale, *Nature* 439 (2006) 707–710, <http://dx.doi.org/10.1038/nature04465>.
- [12] R. Bakish, W.D. Robertson, Galvanic potentials of grains and grain boundaries in copper alloys, *J. Electrochem. Soc.* 103 (1956) 320, <http://dx.doi.org/10.1149/1.2430321>.
- [13] J. Sagripanti, Mechanism of copper-mediated inactivation of herpes simplex virus, *Antimicrob. Agents Chemother.* 41 (1997) 812–817.
- [14] G. Borkow, J. Gabbay, Putting copper into action: copper-impregnated products with potent biocidal activities, *FASEB J.* 18 (2004) 1728–1730, <http://dx.doi.org/10.1096/fj.04-2029fje>.
- [15] A.R. Karlström, R.L. Levine, Copper inhibits the protease from human immunodeficiency virus 1 by both cysteine-dependent and cysteine-independent mechanisms, *Proc. Natl. Acad. Sci. U. S. A.* 88 (1991) 5552–5556.
- [16] D. Wildemeersch, New frameless and framed intrauterine devices and systems – an overview, *Contraception* 75 (2007) S82–S92, <http://dx.doi.org/10.1016/j.contraception.2006.12.023>.
- [17] K.B. Oldham, J.C. Myland, A.M. Bond, *Electrochemical Science and Technology: Fundamentals and Applications*, first ed. John Wiley & Sons, Ltd, Chichester, UK, 2011, <http://dx.doi.org/10.1002/9781119965992>.
- [18] R. Grayburn, Spectroelectrochemical Techniques for the Conservation of Metallic Artefacts (PhD thesis) University of Warwick & Universiteit Gent, 2015.

- [19] A. Adriaens, M. Dowsett, The coordinated use of synchrotron spectroelectrochemistry for corrosion studies on heritage metals, *Acc. Chem. Res.* 43 (2010) 927–935, <http://dx.doi.org/10.1021/ar900269f>.
- [20] M.G. Dowsett, A. Adriaens, Cell for simultaneous synchrotron radiation X-ray and electrochemical corrosion measurements on cultural heritage metals and other materials, *Anal. Chem.* 78 (2006) 3360–3365, <http://dx.doi.org/10.1021/ac052125y>.
- [21] M. De Keersmaecker, M. Dowsett, R. Grayburn, D. Banerjee, A. Adriaens, In-situ spectroelectrochemical characterization of the electrochemical growth and breakdown of a lead dodecanoate coating on a lead substrate, *Talanta* 132 (2015) 760–768, <http://dx.doi.org/10.1016/j.talanta.2014.10.035>.
- [22] J.M. Bastidas, E. Cano, N. Mora, J.L. Polo, Characterization of copper corrosion products originated in simulated uterine fluids and on packaged intrauterine devices, *J. Mater. Sci. Mater. Med.* 12 (2001) 391–397, <http://dx.doi.org/10.1023/A:1011288701499>.
- [23] H. Xue, N. Xu, C. Zhang, Corrosion behavior of copper in a copper bearing intrauterine device in the presence of indomethacin, *Contraception* 57 (1998) 49–53.
- [24] A. Adriaens, M. Dowsett, K. Leysens, B. Van Gasse, Insights into electrolytic stabilization with weak polarization as treatment for archaeological copper objects, *Anal. Bioanal. Chem.* 387 (2007) 861–868, <http://dx.doi.org/10.1007/s00216-006-0835-1>.
- [25] F. Alvarez, P.L. Schilardi, M.F.L. de Mele, Reduction of the “burst release” of copper ions from copper-based intrauterine devices by organic inhibitors, *Contraception* 85 (2012) 91–98, <http://dx.doi.org/10.1016/j.contraception.2011.05.011>.
- [26] E. Chantler, P. Kenway, Z. Larouk, E.B. Faragher, J. Morris, A. Kosonen, et al., An analysis of the corrosion process of the Nova-T IUD. *Adv. Contracept.* 10 (1994) 287–301.
- [27] X.M. He, D.C. Carter, Atomic structure and chemistry of human serum albumin, *Nature* 358 (1992) 209–215, <http://dx.doi.org/10.1038/358209a0>.
- [28] G. Bianchi, P. Longhi, Copper in sea-water, potential-pH diagrams, *Corros. Sci.* 13 (1973) 853–864, [http://dx.doi.org/10.1016/S0010-938X\(73\)80067-8](http://dx.doi.org/10.1016/S0010-938X(73)80067-8).
- [29] D. Scott, J. Podany, B.B. Considine, J.P.G. Museum, G.C. Institute, *Ancient & Historic Metals: Conservation and Scientific Research: Proceedings of a Symposium Organized by the J. Paul Getty Museum and the Getty Conservation Institute, November 1991*, Getty Conservation Institute, Los Angeles, 1994.
- [30] R.W. Corkery, *Artificial Biomineralisation and Metallic Soaps*(PhD thesis) Australian National University, 1998.
- [31] H. Grijalva, M. Inoue, S. Boggavarapu, P. Calvert, Amorphous and crystalline copper sulfides, CuS, *J. Mater. Chem.* 6 (1996) 1157, <http://dx.doi.org/10.1039/jm9960601157>.
- [32] Y. Guo, J. Zhang, L. Yang, H. Wang, F. Wang, Z. Zheng, Syntheses of amorphous and crystalline cupric sulfide nanoparticles and study on the specific activities on different cells, *Chem. Commun.* 46 (2010) 3493–3495, <http://dx.doi.org/10.1039/c001714k>.
- [33] E. Güneri, A. Kariper, Optical properties of amorphous CuS thin films deposited chemically at different pH values, *J. Alloys Compd.* 516 (2012) 20–26, <http://dx.doi.org/10.1016/j.jallcom.2011.11.054>.